

AZZAZI

Anesthesiology, Intensive Care
& Pain Therapy

SPOTLIGHTS ON ANESTHESIA, INTENSIVE CARE & PAIN THERAPY



SECOND EDITION
Vol .1

HESHAM EL AZZAZI

SPOTLIGHTS ON ANESTHESIA, INTENSIVE CARE & PAIN THERAPY

Second Edition

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PREFACE

Response to the first edition of this book has been extremely good. In the years since it was written, positive feedback has come from residents, practitioners, colleagues and others in the medical field.

However, advances and changes in the availability of equipment and drugs, together with changes in clinical practice, made a new edition necessary.

Anesthesiologists are increasingly responsible for the development and care of patients preoperatively and postoperatively and in the recognition and management of those who are critically ill, as well as the continuing essential role that many anesthesiologists play in treating and helping patients live with chronic pain problems. So, as with the first edition, the overall aim of this book is to present anesthesia and its related skills in terms that will help practitioners worldwide to deal effectively and safely with the needs of surgical, severely ill and critically ill patients.

The second edition of spotlights on anesthesia is presented in a completely colored format, organized into three volumes. Most of the chapters in this edition have been completely rewritten (including **1306 new illustrations and images and 500 new tables**), and there are new chapters on physics, anesthetic machines and equipment, pharmacology and pain management. The references have been extensively updated, with emphasis on recent reviews and clinical practice guidelines.

Although this edition has been completely revised, it is still based on the same principles of simplicity and practicability, using many color illustrations and photographs.

The format is designed to provide easy access to information presented in a concise manner. I have tried to eliminate as much as possible superfluous material. The style of the chapters varies. This is deliberate; some relate more to basic principles, physiology, pharmacology, etc. Others are more practical in nature, discussing the principles of anesthetic techniques for certain high-risk situations.

To reduce the variability that is the bane of multi-author texts, I am the sole author and I have personally edited every chapter in this book, to ensure consistency of style. Consequently, this book is a reflection of the workload involved that has taken me four years to complete.

I would really appreciate your feedback on my book. I am sure that even after careful review and editing, it won't be free of errors or perfectly clear to everyone who reads it. If you see ways that I can correct or improve the book, please let me know by e-mail at: hesham@azzazianesthesia.com. If you like certain aspects of the book, I would appreciate hearing about that, too.

Finally, I would like to say that trained people are the most valuable resource in medicine, and what you practice is what you read and learn.

So, if this book helps in any way, in improving the level of training, knowledge and practicing of anesthesia among anesthesiologists, then it will have fully achieved its goal.

Hesham El-Azzazi

DEDICATION

*To all my family, to my wife and lovely children,
Ahmed and Hana and to the souls of my beloved ones*

ACKNOWLEDGMENT

I would never have been able to complete this book without the friendship, support and knowledge of all my professors and colleagues. Every day, I feel how lucky I am to have been able to work with them.

Thanks to my residents and students, who drive me to improve with every minute, and my sincere appreciation to all my patients as well.

I am specially grateful to *Dr. Ahmed El Hanafi*, for his meticulous work with the illustrations, to *Dr. Sahar Talat* for her linguistic efforts, and *Dr. Lobna Habib* for reviewing all radiological material enclosed in this book.

I would also like to thank the readers of the first edition of this textbook who offered me excellent feedback that helped me add several new features to this edition.

Finally, thank you to my family, my wife and children. Thank you for reminding me daily how beautiful the world is, – even after a disenchanting day at work.


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THE HISTORY OF ANESTHESIA

1

- In ancient times “Pharos”
- In Greek and Roman medicine
- Anesthesia practice in Arabic-Islamic medicine

- In modern times, the pioneers of anesthesia
- The term “Anesthesia”

1

In Ancient Times “Pharos”

A-General Anesthesia:

- **Imhotep** (lived about 2600 BC):

He was an ancient Egyptian priest, officer, and builder who was credited as the architect of the earliest of all Egyptian pyramids and the first physician in the world. He is considered to be **the father of medicine**. Imhotep diagnosed and treated over 200 diseases; 15 diseases of the abdomen, 11 of the bladder, 10 of the rectum, 29 of the eyes, and 18 of the skin, hair, nails, and tongue. Imhotep treated tuberculosis, gallstones, appendicitis, gout, and arthritis. He also performed surgery and practiced some dentistry. He extracted medicine from plants. He also knew the position and function of vital organs and circulation of the blood system. **He was familiar with the pulse.**

The Encyclopedia Britannica says “The evidence offered by Egyptian and Greek texts support the view that Imhotep’s reputation was very respected in early times... his prestige increased with the lapse of centuries and his temples in Greek times were the centers of medical teaching” (figure 1-1).

- The ancient **Egyptians** used the combination of opium poppy (morphine) and hyoscyamus (hyoscyamine and scopolamine); a similar combination, morphine and scopolamine, is still used parenterally for premedication (figure 1-2, 1-3, 1-4, 1-5, 1-6, and 1-7).



Figure 1-1: Imhotep



Figure 1-2: A picture on the wall of an ancient Egyptian Pyramid showing circumcision done on awake patients. One of them was restrained by a second person while the other patient was not



Figure 1-3: Needles of ancient Egyptians in the Egyptian Museum in Cairo.

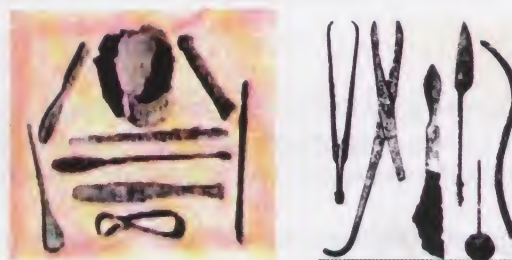


Figure 1-4: Other surgical instruments of ancient Egyptians in the Egyptian Museum in Cairo



Figure 1-5: Ebers (left) and Edwin (right) Papyri of ancient Egyptians where surgical, medical, and pharmacological methods as the use of opium in surgery were mentioned

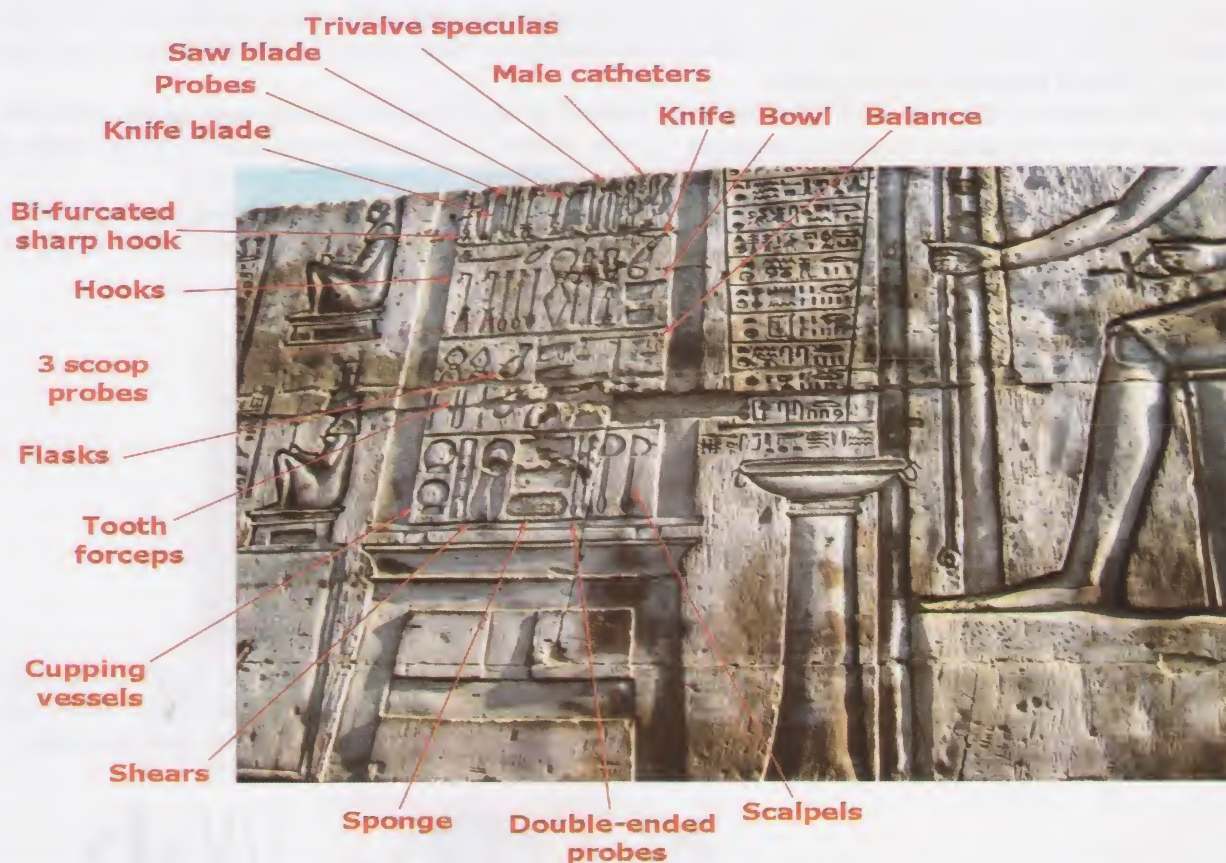


Figure 1-6: Surgical instruments from the outer wall of the Temple of Kom Ombo. The Egyptians used different tools such as knives, saws, hooks, drills, forceps, pinchers, scales, spoons, probes, scalpels, and needles that are present in the Egyptian museum in Cairo. These tools are mentioned in Ebers papyrus

- **Skull trepanning** was one of the first surgical procedures performed in the ancient Egypt. It was performed on live patients to relieve intracranial pressure and to treat fractured skulls (figure 1-8).

B-Regional Anesthesia:

In ancient times, it consisted of compression of nerve trunks (nerve ischemia) or the application of coldness (cryoanalgesia).



Figure 1-7: Nefertiti presenting opium to her husband in a picture of ancient Egyptian pyramid. His leg was broken as seen in the figure.



Figure 1-8: An ancient skull with trepanning

In Greek and Roman Medicine

- In 23-79 A.D., they used decoction of mandrake in alcohol. The juice of mandrake was administered in doses proportional to the strength of the patient. This juice had a narcotic effect. It was given before incisions or punctures were made in the body to ensure insensibility of pain.
- By time, opium (of ancient Egypt) and mandrake (of Roman) fell into the neglect of history.

Anesthesia Practice in Arabic-Islamic Medicine

- Arabic translations of the Greek medicine helped to make Islamic physicians supreme in the middle ages. Al Zahrawi, Ibn Al Nafis, Avicenna, and Ibn Al Koff, were the most famous surgeons in Arabic ages.
- Al Zahrawi described many surgeries and pictured many surgical instruments, which were recently reproduced on Tunisia and held in a surgical museum (figure 1-9).

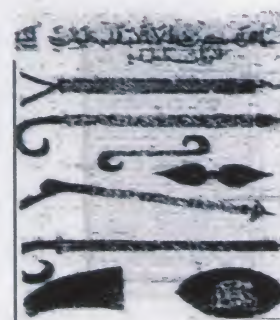


Figure 1-9: Surgical instruments from the Arabic ages

- In his writing, Avicenna indicated that a patient who wanted to have an amputation of one of his limbs must have a drink prepared from a mixture of mandragora and other sleeping drugs.
- Both Mandrake plant and opium plant were written in many of Arabic medical manuscripts (figure 1-10).
- **Ibn Al Koff** (1232-1286 AD) wrote a complete chapter on pain relief in his book '*Al-Omdah fi Sinaet Al-Jeraha*' (Figure 1-11). He differentiated between true and non-true pain relief considering non-true pain relief the 'Anesthetic', which the surgeon may use for treatment of pain, or to be able to institute the surgical treatment.

The technique of use of '**Soporific Sponge**' was purely Arabic and was not known before. The '**Soporific Sponge**' was put in the juice of hashish, papaver, and hyocyamine, and then dried under the sun. When called upon for use, it was humidified again, and placed at the patient's nose; so that the mucus

membrane absorbs it (it is presumed to cause deep sleep and relief of surgical pains). The discovery was introduced into Europe and was practiced until the 18th century when modern inhalational anesthetics were introduced in the 40s of the 19th century (figure 1-12).

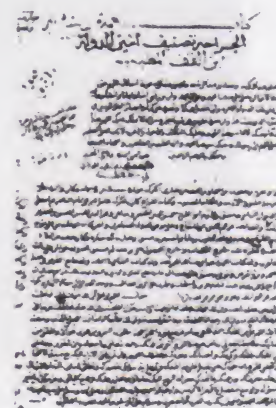


Figure 1-10: Mandrake plant (left) and opium plant (right) from Arabic medical manuscript in Istanbul

Figure 1-11: The first page of Ibn Al-Koff's mosque. Al-Omdah fi Sinaaet Al-Jeraha



Figure 1-12: Inhalational anesthesia in Arabic-Islamic medicine

- The major books, which were followed in the medical and surgical practice, were:
 - Avenicenna's Al-Canon,
 - Al-Razi's Al-Hawi,
 - Ali Ibn Al-Abbas's Al-Kamel,
 - Al-Zahrawi's Al-Tasreef,
 - and - Ibn Al-Koff's Al-Omdah fi Sinaaet Al-Jeraha.

In modern times, the pioneers of anesthesia

1- William Thomas Green Morton, British:

- On October 16th 1846, he used diethyl ether vapor, in a public demonstration, to produce anesthesia on a patient named "Edward Gilbert Abbott" for excision of a neck mass by The Dean of American surgery John C. Warren in Massachusetts General Hospital in Boston (figure 1-13). Soon the news spread reaching the entire Globe. Within 6 months, a similar demonstration in London was done and then in Australia 8 months later.

2- John Snow: (1813-1858), British.

- He is generally considered **the father of anesthesia**, as he made the art of anesthesia a science.
- He was the 1st physician to be a full time anesthetist.

- He described the physiology of general anesthesia and the 5 stages of anesthesia as he was interested in ether.
- In 1847, he published the 1st book on general anesthesia, "On the Inhaler of Ether".
- In 1853, he acted as an anesthetist at the birth of Queen Victoria's eighth child, Prince Leopold and again in 1857, at the birth of Princess Beatrice by usage of the chloroform.
- In 1858, he published his 2nd book, "On Chloroform and Other Anaesthetics".

3- Joseph T. Clover: (1825-1882), British.

- He took Snow's place after Snow's death as England's leading physician anesthetist.
- He emphasized continuously on monitoring the patient's pulse during anesthesia; a practice that was not widely accepted at that time.
- He was the 1st to - use the jaw-thrust maneuver for airway obstruction.
 - have resuscitation equipment always available during anesthesia.
 - use a cricothyroid cannula (to save a patient with an oral tumor who developed complete airway obstruction).

4- Sir Frederick Hewitt: (1857-1916), British.

- He had many inventions including the 1st practical machine for giving N₂O and O₂ in fixed proportions (1887) and the oral airway (1908).
- He wrote the 1st true textbook of anesthesia in 1893.



Figure 1-13: Robert Hinkley's painting from 1882 depicts the first ether anesthetics, provided in 1846, in Boston, Massachusetts. William T.G. Morton (left) is holding the globe inhaler, while the surgeon, John C. Warren operates on the patient, Gilbert Abbott (with permission).

5- Heinrich Friedrich Wilhelm Braun: (1862-1934), German.

- He is called **the father of local analgesia** because:
 - in 1902, he was the 1st to add epinephrine to prolong the action of local anesthetics.
 - in 1905, he was the 1st to use procaine as a local anesthetic and he published **the 1st edition of the textbook "Local Anaesthesia"**.

6- Arthur E. Guedel: (1883-1956), American.

- He was the 1st to elaborate on the signs of general anesthesia after Snow's original description.
- He made an early description of **self-administration of N₂O and air** for obstetrics and minor surgery.
- He advocated cuffed endotracheal tubes.
- He introduced **artificial respiration** during ether anesthesia in 1934.

The Term "ANESTHESIA"

- The Greek philosopher **Dioscorides** (40-90 BC) is said to have first used the term anesthesia in the first century AD to describe the narcotic-like effects of the plant mandragora (An = no, Asthesia = sensation).
- The present use of the term to denote the sleeplike state that makes possible painless surgery is credited to **Oliver Wendell Holmes** in 1846. He suggested this term to William Morton.

Other Historical Points

Tracheal Intubation

6

Airway devices inserted into the trachea were available before the 19th century (about 100 years ago) and were used during resuscitation from drowning. They were also used by otorhinolaryngology specialists such as Chevalier Jackson to remove foreign bodies from the airway by using Jackson laryngoscope. Later on, this procedure was modified by anesthesiologists such as Arthur E. Guedel, Ralph M Waters and Ivan Macintosh.

Neuromuscular Blocking Drugs

The curare poisons were used by the primitive cultures in the Amazonian basin of South America in the early 16th century. The active principle of the poison was derived from the bark of certain lianas (vines) that grew in the primary forests of South America.

In 1812, Charles Waterton (English) took a specimen of the arrow poison to England and determined that a donkey could survive the poison if artificial respiration was provided.

In 1857, Claude Bernard determined that the poison acts on the neuromuscular junction. It was used to treat tetanus and rabies.

In 1942, Harold R. Griffith and Enid Johnson reported their successful use of Intocostin (a drug derived from the curare) poisons to relax abdominal skeletal muscles during cyclopropane anesthesia. In their landmark paper, it was of interest that respiration was not assisted and anesthetic was delivered by mask.

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THE PRACTICE CONDUCT OF ANESTHESIA

2

7

- Balanced anesthesia
- Anesthetic management
- Preoperative management:
- Establishment of Rapport (Doctor-patient relationship)
- Preoperative history
- Physical examination
- Investigations and laboratory evaluation
- Risk assessment
- Informed consent
- Preoperative patient preparation
- Premedications

- Intraoperative management: Patient monitoring
- Patient position
- Choice of anesthesia
- Induction of general anesthesia
- Airway management
- Maintenance of general anesthesia
- Intraoperative fluid therapy
- Intraoperative complications and management
- Emergence and recovery
- Postoperative management
- Approach of anesthetic management
- Evidence-based anesthesia

Anesthesia is a mixture of both science and art.

Balanced Anesthesia

The concept of balanced anesthesia was introduced by John Lundy in 1926.

It consists of:

- 1- **Narcosis** by anesthetic agents i.e., loss of consciousness.
- 2- **Amnesia** by N_2O i.e., loss of memory (it is replaced now by midazolam).
- 3- **Analgesia** by narcotics i.e., loss of pain sensation.
- 4- **Relaxation** by muscle relaxant i.e., loss of muscle tone and activity.

So, the combination of these drugs: - decreases the dose of each and so decreases side effects and - allows the control of each item independently.

Anesthetic Management

It consists of preoperative, intraoperative, and postoperative management.

Preoperative Management

A preoperative visit: is very important.

- If it is not performed by the anesthesiologist, it is considered negligence if anesthetic morbidity or mortality occurs subsequently.
- All data must be written in the preoperative note.

A- Establishment of Rapport (Doctor-Patient Relationship):

- The patient can discuss with the anesthesiologist the possible causes of anxiety regarding the anesthetic and surgical management.
- The anesthesiologist can explain in simple terms the method of anesthesia, the proposed scope of surgery, the informed consent and the postoperative pain relief.

B- The Preoperative History: (including a review of medical records)

It includes:

1- Current Medical Problems and Other Known Problems.

1- Special Habits:

a- **Smoking:** Smoking produces the following effects:

1- The Cardiovascular effects:

- **Blood vessels:** peripheral, coronary, and cerebral vascular diseases.
- **Nicotine** stimulates the sympathetic system causing an **increase in the heart rate** and **arterial blood pressure** and **coronary spasm**.

2- The respiratory effects:

- Carcinoma of lung.
- Chronic obstructive pulmonary diseases.
- Impaired mucociliary function.
- Hyper-active airways.

3- Hemoglobin (Hb): cigarette smoke contains carbon monoxide, which increases carboxy-Hb. In heavy smokers, carboxy-Hb is about 15%. It decreases the availability of O₂ by $\approx 25\%$ and shifts O₂-Hb dissociation curve to the left. The half-life ($t_{1/2}$) of carboxy-Hb is short (4-6 hours); therefore, its withdrawal for 12 hours can increase the arterial O₂ content.

4- Immunity: It impairs the **immune system**.

5- Liver: nicotine is a hepatic enzyme inducer, so it may affect the perioperative analgesic need. Therefore, preoperative cessation of smoking is helpful.

Cessation for • 12 hours decreases carboxy-Hb.

- 2 days can abolish the stimulant effect of nicotine on the cardiovascular system and improve the ciliary function.
- 2 weeks can decrease sputum volume.
- 2 months (this is the ideal time of cessation) can decrease chronic bronchitis (it decreases bronchospasm and bronchial secretions), return the immune system to normal and return the hepatic enzymes to normal.

b- Alcohol Intake:

• **Acute intoxication** enhances the effects of sedatives, opioids, and anesthetics, so **the dose of anesthetic drugs must be decreased**.

• **Chronic alcoholism** induces tolerance to the effects of these drugs due to enzyme induction, so **the dose of anesthetic drugs must be decreased**. Also, chronic alcoholism causes **cardiomyopathy, pancreatitis, liver cirrhosis, and gastritis**.

c- Addiction Drugs as marijuana, cocaine and heroin.

Withdrawal symptoms should be evaluated and managed.

3- Medication History for a- Drug allergy and intolerance.

b- Drug interactions with anesthetics:

Types	Examples
A- Pharmaceutical Drug interaction occurring outside the body e.g., mixed in the same syringe or infusion bag.	1- Thiopental + suxamethonium → inactivate suxamethonium. 2- Thiopental (alkaline) + atracurium (acidic) → inactivation (a precipitate is formed). 3- Ampicillin + glucose or lactate solution → ↓ potency. 4- Penicillin + aminoglycosides → inactivation. 5- Sevoflurane + soda lime → hydrolysis to toxic compounds. 6- Insulin or nitroglycerin binds to the polyvinyl chloride used for the standard i.v. tubing → less amounts of drug are delivered to the patient.
B- Pharmacokinetic 1- At the site of absorption:	1- Iron + antacids → ↓ iron absorption. 2- Iron + ascorbic acid → ↑ iron absorption. 3- Anticholinergics and opioids decrease gastrointestinal motility → ↑ drug absorption. 4- Metoclopramide increases gastrointestinal motility (i.e. a prokinetic drug) → ↓ drug absorption.
2- At transit and storage sites: • Competition for plasma protein binding sites. • Direct interaction of drugs with each other in the plasma or tissues.	• Aspirin, phenylbutazone, or indomethacin → displace warfarin. • Heparin and protamine → inactivation of each other.
3- At the site of metabolism: a- Enzyme induction: these drugs increase the metabolism of other drugs → ↓ their effects b- Enzyme inhibition: these drugs decrease the metabolism of other drugs → ↑ their effects	1- Phenobarbitone, rifampicin, steroids, and phenytoin → ↑ metabolism of warfarin (↑ coagulation), oral contraceptive pills (can cause pregnancy), halothane (can cause severe halothane hepatitis), and isoflurane and enflurane (can ↑ the peak of fluoride level in plasma). 2- Chronic alcoholism or smoking → ↑ i.v. anesthetic metabolism, so ↓ their effect. 1- Chloramphenicol, erythromycin, isoniazid, Ca ⁺⁺ channel blockers, ketoconazole and cimetidine → ↓ metabolism of warfarin, phenytoin, oral hypoglycemics, and β blockers. 2- Monoamine oxidase inhibitors (MAOIs) → ↓ metabolism of opioids, barbiturates, and tricyclic antidepressants. 3- Drugs metabolized by the plasma cholinesterase (e.g., etomidate, methotrexate, cyclophosphamide, ester local anesthetics, mivacurium, or MAOIs) → ↓ plasma cholinesterase availability → ↑ suxamethonium action. 4- Anticholinesterases inhibit plasma cholinesterase → ↑ suxamethonium action.

4- At the site of excretion:	1- Alkalinization of the urine e.g., by NaHCO_3 , Na citrate, or carbonic anhydrase inhibitors → ↑ excretion of acidic drugs (such as aspirin and barbiturate toxicity). 2- Acidification of the urine e.g., by ammonium chloride, arginine HCl, or ascorbic acid → ↑ excretion of alkaline drugs (such as pethidine and amphetamine toxicity).
C- Pharmacodynamic At the site of action (e.g., receptor) or nearby 1- Synergistic: it is either: • Summation or additive effect i.e. $1+1 = 2$ (drugs have the same mechanism of action). • Potentiation or supra-additive effect, the combined action is more powerful i.e. $1+1 = 3$ (drugs have different mechanisms of action).	1- Opioids, benzodiazepines, N_2O , sympatholytics (methyl dopa, reserpine, clonidine), chronic amphetamine, barbiturates, ketamine, local anesthetics (except cocaine), acute alcohol toxicity, or lithium + volatiles → ↓ MAC. 2- Aminoglycosides, polymyxin, clindamycin, volatiles, antiarrhythmics (quinidine, lidocaine, Ca^{++} channel blockers, procainamide), local anesthetics, or Mg sulfate + muscle relaxants → ↑ relaxation. 3- Adrenaline + volatiles → ↑ arrhythmias of both. 4- β blockers and Ca^{++} channel blockers → ↑ the depressant effect of anesthetics → ↓ MAC. 5- Tricyclic antidepressant drugs (they block the reuptake of norepinephrine, serotonin, dopamine at the presynaptic nerve ending) + Opioids especially meperidine → ↑ analgesia and respiratory depression. + Barbiturates → ↑ sleeping time. + Anticholinergics → ↑ central and peripheral activity as they have central anticholinergic action. + Sympathomimetics → ↑ the effect of direct acting drugs (and sometimes indirect drugs) (e.g., hypertension), so they are avoided with epinephrine containing local anesthetics, pancuronium, and ketamine. + Epileptogenic drugs as enflurane → ↓ seizure threshold. 6- MAOIs (especially type A) (they irreversibly inhibit monoamine oxidase type A therefore, they prevent deamination of tyramine, serotonin, norepinephrine, and dopamine) + Opioids especially meperidine → excitatory serotonergic syndrome (i.e., autonomic nervous system instability with hypertensive crisis, tachycardia, diaphoresis, hyperthermia, agitation, hyperreflexia, fits, and coma) then finally respiratory depression and death (it is one of the most fatal drug interactions). + Barbiturates → ↑ sleeping time. + Anticholinergics → ↑ central activity. + Sympathomimetics (especially indirect) → ↑↑ the effect of indirect acting drugs (that may cause hypertensive crisis). → ↑ the effect of direct acting drugs. → ↑ the effect of dopamine. Therefore, they are avoided with epinephrine containing local anesthetics, pancuronium, and ketamine. + High tyramine food as beer or smoked or aged food → severe hypertension, fever, and sweating. + Volatiles → muscle stiffness, hyperpyrexia (halothane in animals). + Suxamethonium → ↑ the duration of the block (phenelzine decreases plasma cholinesterase activity).
2- Antagonism:	1- β agonists + β blockers. 2- α agonists + α blockers. 3- Morphine + naloxone. 4- Benzodiazepines + flumazenil. 5- Muscle relaxant + prostigmine. 6- Indirect acting sympathomimetics and tricyclic antidepressants antagonize antihypertensive drugs. 7- Sympathomimetics (ephedrine), acute amphetamine toxicity, chronic alcoholism or cocaine + volatiles → ↑ MAC.

Drug interactions with nutraceuticals and herbal medicines are discussed later.

N.B.: Mono-amino Oxidase Inhibitors (MAOIs):

a- Type A Inhibitors: e.g., phenelzine (*Nardil*), tranylcypromine (*Parnetil*, or *parnate*) and isocarboxazid. They non-selectively and irreversibly inhibit MAO type A (and B) enzymes.

Precautions: (MAOI- Safe anesthetic)

- 1- If elective surgery is indicated, stop MAOIs 2-3 weeks before anesthesia because these agents are irreversible. This time allows regeneration of new enzymes. Replace MAOIs by other antidepressants.
- 2- If an urgent or emergent procedure is indicated or patients develop severe or refractory psychiatric disease on MAOIs discontinuation; therefore,

- Avoid indirect acting pressors and serotonin agonists or antagonists.
- Administer opioids cautiously as patients are sensitive to them. Fentanyl and morphine are considered safe.
- Avoid meperidine, pentazocine, and tramadol.

- Benzodiazepines are used as sedatives.
- Avoid sympathetic stimulations such as light anesthesia, topical cocaine spray, injection of indirect-acting vasopressors.
- I.v. induction agents are safe but ketamine (a sympathetic stimulant) should be avoided.
- Succinylcholine dose should be decreased because phenelzine decreases serum cholinesterase activity.
- Inhalational anesthesia and nitrous oxide are used safely but anesthetic requirements may be increased due to increased concentrations of norepinephrine in the central nervous system.
- Non-depolarizing muscle relaxants are considered safe except pancuronium, which may show exaggerated tachycardia.
- Spinal or epidural anesthesia is acceptable, although the potential of these anesthetic techniques to produce hypotension and the consequent need for vasopressors may make an advantage for general anesthesia. The addition of epinephrine to local anesthetic solutions should probably be avoided.

3. **If hypotension occurs**, the patient should be given i.v. fluids and a direct acting vasopressor agent such as phenylephrine.

If hypertension occurs, direct acting drugs or direct acting adrenal antagonists should be used.

4. Use newer MAO-A inhibitor drugs that act in a reversible fashion and allow safe anesthesia if discontinued for less than 2 weeks e.g., moclobemide.

b- Type B Inhibitors: e.g., selegiline.

They selectively inhibit MAO-B, which is not responsible for the breakdown of epinephrine, norepinephrine, metanephrine, or serotonin, so during anesthesia no complications occur as those occurring with MAO-A inhibitors. Type A monoamine oxidase is present primarily in the gastrointestinal tract, which is not inhibited by selegiline; therefore, selegiline is not associated with tyramine-associated hypertensive crisis. It is still recommended to avoid administering meperidine to a patient taking selegiline.

N.B.: α Agonists and β Blockers Interaction

There are many conditions in anesthesia where α agonists and β blockers can be administered simultaneously such as:

- accidental overdose of phenylephrine or epinephrine (e.g., epinephrine containing local anesthetics) in patients receiving long term β blockers
- or • an overdose of phenylephrine or epinephrine wrongly treated by β blockers.

These conditions may cause **congestive heart failure, pulmonary edema, and cardiac arrest**.

Explanation: an overdose of phenylephrine or epinephrine causes:

- severe α agonist action i.e., vasoconstriction (hypertension).
- β_1 activation i.e., tachycardia.

This is accompanied by β_2 activation i.e., peripheral vasodilatation.

With β blockers (either as in concomitant treatment or treatment of an overdosage), β receptor blockade occurs causing unopposed α action. The latter produces severe vasoconstriction, which leads to irreversible congestive heart failure, pulmonary edema, and cardiac arrest.

This condition is treated with **glucagon** (to reverse the cardiovascular response to beta-blockers), as isoprenaline (*Isopril*), epinephrine, and dopamine will be ineffective.

The dose of glucagon is 5-10 mg in adults, 1 mg in children + 1-5 mg/h infusion.

Treatment:

1- Treatment of overdosage of phenylephrine or epinephrine:

a- If mild to moderate hypertension occurs, it is left untreated as it is transient (usually 10-15 minutes).

β blockers, Ca^{++} channel blockers and high concentrations of inhalational agents should be avoided.

b- If severe hypertension occurs, that can cause end organ damage especially myocardial ischemia, it is treated by:

- α antagonists as phentolamine (*Regitin*).

- Direct vasodilators as Na nitroprusside (*Niprid* or *Nipruss*).

Q: Discuss anesthetic drug interactions with mood-stabilizing drugs?

A: Mood-stabilizing drugs include tricyclic antidepressants, MAOIs, and lithium.

c- **History of nutraceuticals and herbal medicines:**

- Nutraceuticals are defined as herbs, dietary ingredients, and dietary supplements (a product used to supplement the diet) e.g., vitamins, minerals, amino acids, enzymes, and organ tissues...etc.
- It is important to ask your patients about their use of any of these products, particularly ones that are not taken in pill or tablet forms. Many patients do not realize that teas and other forms of herbs can be just as deadly, particularly when mixed with other medications such as anesthetic drugs.
- These products are not under control or with Food and Drug Administration (FDA) approval.

- Many patients believe that the herbs and dietary supplements that are taken are safe because they are natural; this is, of course, the wrong idea.
- The American Society of Anesthesiologists recommends in 1999 that patients taking any dietary supplement should discontinue them, 2 weeks before any surgical procedure.

Name	Alleged benefits	Effects during anesthesia	Recommendations
Echinacea (<i>Immulant</i>)	Immune system stimulation	<ul style="list-style-type: none"> • Allergic reactions. • Hepato-toxicity. • Interference with immune suppressive therapy (e.g., with organ transplants). 	<ul style="list-style-type: none"> • Should be discontinued as early as possible before the surgery.
Ephedra (ma huang)	Promotion of weight loss.	Ephedrine-like sympathetic stimulation with increased heart rate and arterial blood pressure, arrhythmias, myocardial infarction, and stroke.	<ul style="list-style-type: none"> • Should be discontinued at least 24 hours before surgery. • Avoid MAOIs.
Garlic (ajo)	Reduction of blood pressure and cholesterol levels	Inhibition of platelet aggregation (irreversible).	<ul style="list-style-type: none"> • Should be discontinued at least 7 days before surgery.
Ginkgo (duck foot, maidenhair, silver apricot)	Improvement of cognitive performance (e.g. dementia). An increase in peripheral perfusion (e.g. impotence, macular degeneration)	Inhibition of platelet activating factors.	<ul style="list-style-type: none"> • Should be discontinued at least 36 hours before surgery.
Ginseng	Protection against stress.	Hypoglycemia, inhibition of platelet aggregation and coagulation cascade.	<ul style="list-style-type: none"> • Should be discontinued at least 7 days before surgery.
Kava (kawa, awa, intoxicating pepper) (<i>Kava, Dormival</i>)	Reduction of anxiety	GABA-mediated hypnotic effect may need to decrease MAC.	<ul style="list-style-type: none"> • Should be discontinued at least 24 hours before surgery.
St. John's wort (amber, goatweed, hypericum perforatum, klamath-weed)	Treatment of mild to moderate depression	Inhibits catecholamine reuptake by neurons.	<ul style="list-style-type: none"> • Should be discontinued at least 5 days before surgery
Valerian	Reduction of anxiety	GABA-mediated hypnotic effect may need to decrease MAC.	<ul style="list-style-type: none"> • Taper the dose weeks before surgery.

4- History of Previous Anesthesia, Surgery and Obstetric Deliveries:

To detect previous anesthetic problems e.g., succinylcholine apnea, halothane exposure within 6 months.

5- Family History:

To detect hereditary and pharmaco-genetic conditions associated with anesthesia e.g., porphyria, malignant hyperthermia, hypercholesterolemia, cholinesterase abnormalities, or myasthenia gravis.

6- Review of Organ Systems: which includes:

- General (including the activity level and exercise tolerance).
- Nervous.
- Gastrointestinal.
- Psychiatric.
- Infections as acquired immune deficiency syndrome (AIDS), or hepatitis.
- Possibility of pregnancy as **pregnancy is a contraindication to elective surgery** because:
 - In early pregnancy, there is a risk of - teratogenic effects (at least theoretically).
 - induction of spontaneous abortion.

In late pregnancy, there is a risk of aspiration.

7- Last Oral Intake.

C- Physical Examination:

It should be documented with the medical history in the medical notes. It includes:

- 1- Vital signs.
- 2- Airway.
- 3- Heart and lung.
- 4- Nervous system.
- 5- Other systems that appear to be affected by the history.

N.B.: - If there is any trauma, search for other traumas.

- If there is any congenital anomaly, search for other congenital anomalies.
- If there is any autoimmune disease, search for other autoimmune diseases.
- In all patients, search for medical problems.

D- Investigations and Laboratory Evaluation:

- It is generally accepted that the **clinical history and physical examination** represent the **best methods** of screening for the presence of diseases.
- Routine laboratory tests in patients who are apparently healthy by clinical history and examination are invariably of little use and a waste of resources.
- Before ordering extensive investigations, the anesthesiologist should consider how the results of these investigations will affect the patient's care and management.
- No test is 100% sensitive and specific; therefore, results must be interpreted in the context of the clinical situation.
- Any disease detected by history or physical examination must be evaluated by more investigations.
- Recommended routine preoperative laboratory evaluation of an apparently healthy patient are:-

1- Complete blood picture (CBC), hematocrit, or Hb concentration:

- All patients > 60 years of age.
- All menstruating females.
- If significant blood loss is expected and/or blood transfusion.
- All Asian patients (for sickle cell anemia).
- Patients with a clinical condition such as history of blood loss, previous anemia, blood diseases, malnutrition, liver diseases, or renal diseases.

2- Serum glucose, serum creatinine, urea, and electrolytes:

- All patients > 60 years of age.
- Patients with history of diabetes, renal, hepatic, nutritional diseases, diarrhea, vomiting, or patients receiving medications as steroids, diuretics, or nephrotoxic drugs.

3- Liver function tests:

- Patients with hepatic or nutritional diseases.
- Patients with history of chronic alcoholism.

4- Coagulation screen:

- Patients with history of coagulation disorders, drug abuse, chronic alcoholism, liver or renal diseases.
- Patients with a suspicious history of bleeding after a wound, previous surgery or with a history of easy bruising.
- Patient receiving anticoagulants as warfarin, heparin, aspirin... etc.

5- Chest x-rays:

- All patients > 60 years of age.
- Patients with history of cardiac, thyroid, respiratory diseases or cancer (for secondaries).

N.B.: Smoking and resolved upper respiratory infection are not indications for a preoperative chest x-ray.

6- Electrocardiograph (ECG):

- All patients > 50 years of age (some authors recommend > 40 years of age).
- Patients with history of cardiovascular diseases, hypertension, or pulmonary diseases.

N.B.: A normal previous trace within 1 year is acceptable unless there is a recent cardiac history.

N.B.: Routine testing for AIDS or hepatitis is highly controversial.

A routine preoperative pregnancy test in women of childbearing period is controversial.

For example: a **20 year healthy adult male** without any past or present medical history, **no preoperative investigations are required** to prepare him for a **minor surgery** without much bleeding such as repair of inguinal hernia.

E- Risk Assessment

It is detection of pre-, intra-, and postoperative risk factors which increase mortality and morbidity.

Over a broad range of surgeries and patient ages, the overall mortality rate from surgery is 0.6%. This is several times greater than the overall mortality rate attributable to anesthesia per se ($\approx 0.001\%$).

I) General Scoring Systems:

Are designed to predict non-specific undesirable events:

a- ASA Physical Status Classification:

- It was first recommended by the American Society of Anesthesiologists in 1961.
- It should be applied to all patients who present for surgery although it does not embrace all aspects of anesthetic risks such as age and difficult intubation.

It was originally 5 classes. A 6th category was later added to address the brain-dead organ donor.

Class	Definition	Perioperative Mortality Rates
I	This class includes a normal healthy person.	~ 0.1 % It represents a "green flag" for treatment.
II	This class includes a patient with mild to moderate systemic disease and no functional limitations or a patient ASA 1 who demonstrates a more extreme anxiety and fear towards surgery. Examples; well-controlled non-insulin controlled diabetes, epilepsy, asthma, and/or thyroid conditions; ASA I with a respiratory condition, pregnancy, and/or active allergies.	~ 0.2 % It represents a "yellow flag" for treatment.
III	This class includes a patient with moderate to severe systemic disease that results in some functional limitations. Examples: angina pectoris, myocardial infarction or cerebrovascular accident history, insulin dependent diabetes, congestive heart failure, chronic obstructive pulmonary disease.	~ 1.8 % It represents a "yellow flag" for treatment.
IV	This class includes a patient with severe systemic disease that is a constant threat to life and functionally incapacitating. Examples: unstable angina pectoris, myocardial infarction or cerebrovascular accident within the last six months, high blood pressure, severe congestive heart failure or chronic obstructive pulmonary disease, uncontrolled epilepsy, diabetes, or thyroid condition.	~ 7.8 % It represents a "red flag" for treatment.
V	This class includes a moribund patient who is not expected to survive 24 hours with or without surgery. These patients are almost always hospitalized, terminally ill patients. Emergency care, in the realm of palliative treatment may be necessary.	~ 9.4 %
VI	This class includes a brain-dead patient whose organs are being harvested.	
E	If the procedure is an emergency , the physical status is followed by suffix E e.g., 3E).	

b- POSSUM:

It is the Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity. It was recommended in 1991. It should be applied in the immediate preoperative period.

Aim: it is done to compare mortality and morbidity over a wide range of general surgical procedures rather than to predict mortality for an individual.

It consists of:

Physiological Factors	Operative Factors
<ul style="list-style-type: none"> • Age (years) • Cardiac status • Respiratory status • Systolic blood pressure • Pulse rate • Glasgow coma scale • Hemoglobin concentration • White cell count • Serum sodium concentration • Serum potassium concentration • ECG rhythm 	<ul style="list-style-type: none"> • Operative complexity • Single vs. multiple procedures • Expected blood loss • Peritoneal contamination (blood, pus, bowel content) • Extent of any malignant spread • Urgency of surgery

P-POSSUM: is a modified POSSUM. It was recommended because the original POSSUM was claimed to overestimate the risk of death in low-risk patients.

V-POSSUM: is a speciality-specific variant that is used for elective vascular surgery.

There are other speciality-specific variants for other types of surgeries.

O-POSSUM: is a modified POSSUM made where "O" indicates oesophago-gastric. It is especially weighted for upper gastro-intestinal surgery.

II) Specific System Assessment:

That focuses on prediction of specific morbidity or technical difficulty.

- 1- Cardiovascular assessment e.g., Goldman's index of cardiac risk in non-cardiac procedure.
- 2- Respiratory assessment.
- 3- Neurological assessment.
- 4- Renal and liver disease assessment.

F- Informed Consent

• Informed consent means to ensure that the **competent patient (or guardian)** has **sufficient information** about the procedure (both anesthetic and surgical) and its risks in a **lay plain terms and language** to make a reasonable and prudent decision whether to consent or not **without pressure**.

• **The competent patient:** is an adult patient who is able to make decisions on his/her own about his/her treatment after understanding and weighing the risks and benefits to arrive at a balanced choice. For a competent patient, no other person can consent or refuse treatment on his/her behalf.

When the patient is a minor or otherwise not competent to consent, the consent must be obtained from someone legally authorized to give it, such as a parent, guardian or close relative.

The age of a minor is different according to each country as some countries consider less than 16 a minor.

• **The content of the informed consent:**

▫ Regardless of the anesthetic technique chosen (as regional, local, topical or sedative), the consent must always be obtained for **general anesthesia** in case other techniques prove inadequate.

▫ A **description** of the proposed anesthetic and surgical procedure.

▫ The **common complications** associated with the proposed anesthetic and surgical techniques (e.g., succinylcholine pains, postdural puncture headache, damage to loose or crowned teeth, numbness or weakness if a local or regional technique is to be used...etc). Very rare complications are not necessary to be mentioned. It is generally advisable to inform the patient that some complications may be life-threatening.

▫ Clear information if a **technique of a sensitive nature** (e.g., insertion of an analgesic suppository) is to be used during anesthesia or surgery.

• **The time of consent signing:**

▫ **Enough time** should be left to the patient to think and ask questions about the procedure to make a good decision.

▫ It should be performed **before sedating** the patient.

• **Types of the consent:**

Although oral consent may be sufficient, written consent is usually advisable for medicolegal purposes.

• **Importance of the consent:** If any procedure is performed without the patient's consent, the physician may be liable for assault and battery.

In an emergency, life-saving procedures can be done without a patient's consent.

G- Preoperative Patient Preparation:

• Generally;

- **In elective surgery**, if there is any medical condition which may be improved (e.g., pulmonary diseases, hypertension, cardiac failure, renal disease, shock, and diabetes) **surgery should be postponed** and appropriate managements should be instituted **until resolving the acute attack or improving the chronic condition** to reach its best state.

- **In emergency surgery**, the operation may be **postponed only for 1-2 hours** to permit restoration of circulating blood volume but **if hemorrhage is extensive and continuous surgery should be performed without any postponement**.

• **Complicated medical problems** may require **consultations with other specialists**.

• Blood products, intensive care bed, or any other equipment must be available during the preoperative period if this is thought necessary.

• **Preoperative fasting:**

a) **For elective surgery** (preoperative NPO "nil per os")

ASA recommendations apply only to healthy patients for elective surgery (it is not applied to women in labor).

Type	Minimum Fasting Hours (for all ages)
• Clear fluids (water, fruit juices without pulp, carbonated beverages, clear tea, or black coffee) but not alcoholic drinks; up to 10 mL/kg.	2 hours as this decreases gastric contents and acidity compared to 6 hours preoperative fasting.
• Breast milk	4 hours
• Infant formula.	4-6 hours
• Non-human milk.	6 hours
• Light meals (toast and clear fluids, but avoid meals containing fried or fatty foods).	6- 8 hours
• Fried or fatty foods or large meat content (should be avoided)	> 8 hours because they prolong the gastric emptying.
• Oral medications.	1-2 hours with sips of water up to 150 ml.

• **Preoperative fasting does not ensure an empty stomach** because:

- The normal daily gastric secretion is about 2000 ml in adults; consequently, the stomach is never truly "empty".

- Solid food passes through the stomach at variable and unpredictable rates, sometimes taking up to 12 hours especially if a high fat content is present. Conversely, clear liquids have a 50% emptying time of just 12 to 20 minutes.

It was found that 12-80% of patients scheduled for an elective surgery have a gastric volume of > 0.4 ml/kg and a pH of < 2.5 .

b) For emergency surgery:

The stomach should be emptied by either:

- physical means as a large bore **naso-gastric tube** which is withdrawn before induction of general anesthesia.
- pharmacological means: as **metoclopramide** (*Plasil*), **cimetidine** (*Tagamet*), or **ranitidine** (*Zantac*).

The best guidelines are as follows:

- 1- Elective surgery should be postponed till 6 hours of ingestion of solid food.
- 2- One cup of clear fluids is permitted and encouraged 2 hours before surgery.
- 3- Metoclopramide, H_2 blockers, antacids and antiemetics are administered only to patients at increased risk of aspiration. They are not used routinely as studies showed no decrease in the incidence of aspiration with or without them.

H- Premedications:

Definitions:

It is administration of drugs in the preoperative period before induction of anesthesia by:

- 1-5 minutes for i.v. drugs,
- 30-60 minutes for i.m. drugs,
- and 60-90 minutes for oral drugs,

They include:

1- Benzodiazepines: they are used for:

a- Anxiolysis:

It is decreasing anxiety and fear **without decreasing the level of consciousness**; it is only measured by the patient.

It is the main goal and essential for nearly all patients. It is the only essential premedication.

N.B.: **Psychotherapy** via doctor-patient relationship is the most important anxiolytic.

b- Sedation:

It is decreasing activity and excitement **with decreasing the level of consciousness**; the patient may appear to an observer adequately sedated but on questioning may be quite anxious.

Generally, decrease or omit sedation if there are critical conditions such as heart failure, liver cell failure, renal failure, increased intracranial tension, or impending airway obstruction.

c- Anterograde amnesia:

It is loss of memory for events after administration of the drug.

Lorazepam produces amnesia more than diazepam. It is important especially in pediatrics.

N.B.: The barbiturates and to a lesser extent the opioids produce sedation without anxiolysis.

2- Anticholinergics: they are used for;

a- Antisialagogue: (i.e., a decrease in salivary secretions).

It is especially indicated, if fiberoptic intubation, ketamine, or ether anesthesia is planned.

b- To decrease vagal reflexes:

It is indicated especially in • Eye muscle traction especially medial rectus.

- Repeated suxamethonium.
- Induction with halothane in pediatrics.
- Opioid/relaxant techniques with surgical stimulation.
- Propofol anesthesia in patients with a slow heart rate.

3- Antiemetics: e.g., metoclopramide, ondansetron...etc.

They are indicated to decrease postoperative nausea and vomiting especially after opioid administration and biliary tract surgeries.

4- Prophylaxis against Aspiration:

a- Reduction of gastric volume e.g., metoclopramide.

b- Elevation of gastric pH e.g., sodium citrate.

They are especially indicated in obstetric and emergency patients.

5- Antihistaminics (H₁ blockers):

They are used to prevent allergic reactions.

6- Opioids: they are used to produce:

a- **Blunting of sympatho-adrenal responses** such as the pressor response of intubation.

They are especially indicated in ischemic heart or hypertensive patients.

N.B.: A β blocker or clonidine can also be used.

b- **Analgesia**, if there is preoperative pain.

c- **Sedation** (without anxiolytic effects):

7- Others:

As antibiotics (should be received within 1 hour of the incision), anticoagulants, corticosteroids, bronchodilators, non-steroidal anti-inflammatory drugs (NSAIDs), and COX₂ inhibitors may be indicated.

Intraoperative Management**Intraoperative Anesthetic Record**

Values:

- 1- A useful intraoperative monitor.
- 2- A reference of the patient for future anesthesiologists.
- 3- Important for medico-legal purposes.
- 4- A tool for quality assurance.

Before induction of anesthesia, anesthesiologists must

- perform a preoperative check of the anesthesia machine and other equipment.
- perform a preanesthetic check of the correct patient for the correct operation.
- reevaluate the patient immediately prior to induction including history, examination, investigation, consultations, and consent.
- apply the premedications.

Intraoperative management includes

I- Patient Monitoring:

The standard recommended monitors are 3 or 5 lead ECG, noninvasive blood pressure (NIBP), pulse oximetry, and endtidal CO₂.

Other special monitors are indicated according to the medical condition of the patient.

II- Patient Position:

General anesthesia is induced in a supine horizontal position, and then the patient position is readjusted according to the type of surgery which may be:

- Supine: horizontal, trendelenburg or reverse Trendelenburg.
- Prone.
- Lithotomy.
- Lateral.
- Sitting.

These positions are discussed later.

III- Choice of Anesthesia:

It may be general, regional, local, or combined anesthesia.

IV- Induction of General Anesthesia:**a- Intravenous Induction:**

Types and Indications:

- **Smooth i.v. induction:** is indicated in most **routine purposes** by using an i.v. agent and a non-depolarizing muscle relaxant
- **Rapid sequence (crash) induction:** is indicated in patients with a **full stomach** by using an i.v. agent and depolarizing muscle relaxant or rocuronium.
- **Modified rapid sequence induction:** is indicated in patients with a **full stomach** but need to **decrease the pressor response** of intubation as hypertensive patients. It is similar to rapid sequence induction with addition of opioids.
- **Cardiac induction:** is indicated in **cardiac surgeries** by using a large dose of opioids and a muscle relaxant to avoid affection of hemodynamics of the patients.

Technique:

- An **i.v. cannula** is inserted at first. A large i.v. cannula is used if blood loss is expected, best in the forearm or the back of the hand. Avoid insertion in antecubital fossa due to the risk of intra-arterial cannulation. In children, EMLA cream (a local anesthetic) can be used.

- After monitors are applied, **preoxygenation** with 100% O₂ by a close-fitting face mask done via the Magill breathing system for 5 minutes (alternatively, 3-4 large breaths "vital capacity" may be used).
- After choosing a suitable i.v. anesthetic induction agent and calculation of the suitable dose, a **small test dose** is administered commonly with observing its effect for early detection of hypersensitivity reactions or intra-arterial injection. **Slow injection** is required especially in patients with a slow circulation time e.g., elderly, hypovolemic, or shocked patients or patients with cardiovascular diseases, with monitoring the effect of drugs on cardiovascular and respiratory systems.
- I.v. induction agents induce rapid transition to stage 3 of anesthesia.

Rapid Sequence Induction:

- Meticulous assessment of the airway is mandatory preoperatively. If difficult intubation is suspected, alternative techniques such as awake fiberoptic intubation should be considered.
- A patient should be on a **tipping trolley or table with an adjustable head piece** to alter the degree of neck extension/flexion quickly.
- Ideally, the patient is put in the **sniffing position** with the neck flexed on the shoulders and the head extended on the neck.
- The optimum position is that in which the anesthesiologist has gained the greatest experience in performing intubation.

Some prefer the **reverse trendelenburg (head-up) position to prevent regurgitation** and others prefer the **trendelenburg (head-down) position to prevent aspiration**.

- A **skilled assistant** should be present to perform cricoid pressure, assist in turning of the patient and supply stylets and tubes.
- A **good suction** apparatus must be within reach of the anesthesiologist's hand.
- **Preoxygenation** with 100% O₂ for 3-5 minutes is mandatory.
- **Cricoid Pressure (Sellick's Maneuver)** (figure 2-1)

It should be done by the right hand of a skilled assistant. The cricoid cartilage is held between the **thumb and middle finger** and firm digital **pressure is exerted mainly with the index finger** over the cricoid cartilage in a posterior direction. Some authors recommend a bimanual technique with the second hand behind the neck. It is difficult to precisely judge the magnitude of downward external pressure. A minimum force of **30 N is required (about 5 kg weight)**. This pressure **compresses the esophagus** between the cricoid cartilage and the vertebral column because the cricoid cartilage forms a **complete ring**. The tracheal lumen is not distorted. Cricoid pressure is applied just before the i.v. agent or as soon as consciousness is lost, and maintained until the cuff of the endotracheal tube is inflated and its correct placement in the trachea is confirmed by auscultation. Intubation is done without waiting.

Validity of Cricoid Pressure:

- Although the application of cricoid pressure is often performed, it is important to recognize that aspiration has occurred during such application and data supporting the efficacy of cricoid pressure are not available.
- An observational study using magnetic resonance imaging revealed that the crico-pharyngeal muscle, rather than the esophagus, was lying posterior to the cricoid in most individuals.
- Furthermore, downward external pressure on the cricoid cartilage may displace the esophagus laterally rather than compressing it and also may displace the airway and compressing it in 70-80% of patients.
- Cricoid pressure may impair the laryngoscopic view of the glottis especially in difficult intubation
- Cricoid pressure may make the insertion of laryngeal mask airway, more difficult and may not be applied successfully.

Therefore, cricoid pressure has not been proven to prevent aspiration, is commonly misapplied, is often difficult to apply in the obese patient with a large neck, and might worsen intubating conditions.

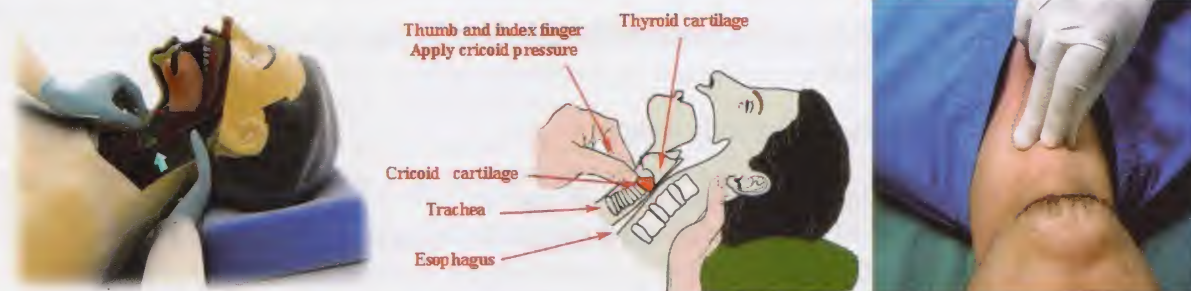


Figure 2-1: Cricoid pressure

b- Inhalational Induction:**Indications:**

- 1- Young uncooperable children without a venous line.
- 2- Upper airway obstruction e.g., epiglottitis.
- 3- Lower airway obstruction e.g., with a foreign body.
- 4- Broncho-pleural fistula or empyema.
- 5- No accessible veins.
- 6- Needle phobic adults.
- 7- Suspecting difficult airway control and ventilation, as if ventilation ceases due to profound airway obstruction, the induction process will be reversed allowing awakening of the patient and regaining control of the airway.

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Technique:

At first, the technique should be explained to the patient (if possible).

- By using either:
 - mask technique: using an anesthetic black mask (better with a clear face mask) or
 - no mask technique: by insufflation of the volatile agent over the face by placing a T-piece in the anesthesiologist's hand (no mask technique).
 - The child can be allowed to sit during the early stages of induction.
 - Start with a mixture of 70 % O₂ and 30 % N₂O then gradually increase N₂O till O₂: N₂O becomes 3: 7 then add the volatile agent in 0.5 % increments every 3-5 breaths.
- If sevoflurane is used, 8% can be inspired directly to achieve more rapid induction than its use incrementally.
- In more cooperative patients, a **single breath technique** is used, as the patient is allowed to take one vital capacity breath from a prefilled 4 liter reservoir bag (in adults) or 2 liter bag (in children) containing high concentration of the volatile agent e.g., halothane 5 % or sevoflurane 8 %. This causes smooth induction within 20-30 seconds.
 - Halothane or **sevoflurane** are used but isoflurane and desflurane are avoided due to their pungent odor, which causes coughing, breath holding and laryngospasm.
 - After consciousness is lost, an i.v. cannula is inserted and intubation is completed either by
 - a muscle relaxant.
 - or - deepening anesthesia by increasing the concentration of volatile agents.
 - N₂O is discontinued before intubation to allow the patient's lung to be filled with high inspired O₂ and produce high O₂ saturation to be maintained during the period of apnea.
 - Avoid positive pressure ventilation before intubation because it may cause gastric distention which impairs lung expansion and induces vomiting and aspiration. If gastric distension occurs, a non-traumatizing naso-gastric tube is used to decompress the stomach.

Disadvantages:

- 1- Slow induction of anesthesia.
- 2- Airway obstruction, bronchospasm, laryngospasm, hiccup, or severe bradycardia. These may occur before an i.v. access is available; therefore,
 - Atropine i.m. 0.02 mg/kg is given for bradycardia (do not exceed 0.04 mg/kg).
 - Suxamethonium i.m. 4-6 mg/kg is given for intubation (do not exceed 150 mg).
- 3- Environmental pollution.

c- Intramuscular Induction:**Indication:**

For an uncooperable combative child.

Technique:

It is performed by ketamine i.m. 5-10 mg/kg + suxamethonium i.m. 4-6 mg/kg (onset 3-4 min).

d- Rectal Induction (Steal Induction):**Indication:**

For an uncooperative child, less than 20 kg body weight.

Technique:

Use either thiopental 30-40 mg/kg or methohexital 25-30 mg/kg 5-10 % solution (given in presence of parents) to induce sleep within 5-10 min, then the child is taken to the operating room for steal induction. It may cause airway obstruction.

V- Airway Management: See later.

11- Maintenance of General Anesthesia:

a- Inhalational Anesthesia with Spontaneous Ventilation:

Indications:

- 1- Procedures which do not need muscle relaxation such as superficial surgeries.
- 2- Minor procedures such as short operations or when little reflexes or pain are expected.

N.B.: it is not suitable for patients at risk of aspiration.

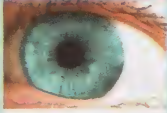
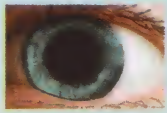

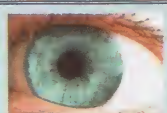


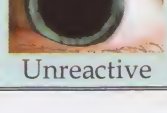
Technique:

- By Magill breathing system with 70 % N₂O in O₂.
- The depth of anesthesia is controlled by volatile agents e.g., halothane 1-2 %, isoflurane 1-2%, or sevoflurane 2-3%. The depth of anesthesia is assessed by signs of inadequate depth of anesthesia (tachypnea, tachycardia, hypertension, sweating, lacrimation and reflex movement in response to surgery).

Airway is maintained using a mask, laryngeal mask airway, or endotracheal intubation.

Guedel's Classic Signs of Anesthesia (Stages of Anesthesia):

These stages are seen in patients premedicated with atropine and morphine and anesthetized by ether in air, but are not so obvious with recent inhalational or intravenous agents.

Stage	Respiration	Pupil Size	Eye Reflexes	Respiration Reflexes
1- Analgesia (by 50% N ₂ O in O ₂)	Regular and small volume		All are present	All are present
2- Excitement (it is passed rapidly during i.v. induction)	Irregular and erratic with breath-holding		Eyelash reflex is absent	
3- Anesthesia Plane I	Regular and large volume	 Central	Eyelids are resistant to lid elevation. Conjunctival reflexes are depressed.	Pharyngeal reflexes, vomiting and gag are depressed. Swallowing is present
Plane II	Regular and large volume		Corneal reflexes are depressed	Laryngeal reflexes are present e.g., anal stretch causing laryngeal spasm
Plane III	Regular, small volume, and diaphragmatic		Lacrimation is absent	Laryngeal reflexes are depressed.
Plane IV	Irregular, small volume, and diaphragmatic			Carinal reflex is depressed
4- Overdose	Respiratory (and cardio-vascular) depression causing apnea	 Unreactive	All brain stem reflexes are depressed then absent	All brain stem reflexes are depressed then absent

b- Relaxant Anesthesia:

Indications:

- 1- Operations that need muscle relaxation e.g., major abdominal operations.
- 2- Major operations as
 - They are lengthy operations (spontaneous ventilation for a long time causes respiratory insufficiency).
 - Much pain is expected.
- 3- Abnormal positions interfering with spontaneous ventilation.

Technique:

- After induction of anesthesia, relaxation is produced by using either:
 - a- A depolarizing muscle relaxant (succinylcholine), followed by a non-depolarizing muscle relaxant after its action subsides.

Or b- A non-depolarizing muscle relaxant is used for intubation. Controlled ventilation, with an inhalational agent in doses less than MAC or total i.v. anesthesia (\pm opioids), is maintained at first manually by compressing the reservoir bag and then by a mechanical ventilator. It is used in case of an elective fasting patient with normal gastric emptying and no history of hiatus hernia or regurgitation. The usage of rocuronium allows rapid intubation without the usage of succinylcholine or face mask ventilation.

It requires reversal of the residual muscle relaxation.

Assessments are needed for:

1- Adequacy of **the depth of anesthesia** and **awareness during anesthesia**, especially if light anesthesia is used as during the usage of small doses of opioids and absence of N₂O or inhalational agents.

2- Adequacy of **muscle relaxation**. It should be assessed either by:

- clinical signs as retraction of wound edges during abdominal surgeries, movement of abdominal, diaphragmatic (hiccup) or facial muscles.

or • a peripheral nerve stimulator.

3- Adequacy of **ventilation**. Signs of inadequate ventilation include venous dilatation, wound oozing, tachycardia, hypertension, and patients' attempts of spontaneous ventilation (i.e., hypercarbia).

Therefore; measurement of airway pressure and end expired PCO₂ are now strongly recommended with relaxant anesthesia and controlled ventilation.

VII- Intraoperative Fluid Therapy: See later

VIII- Intraoperative Complications and Management: See later

IX- Emergence and Recovery:

After discontinuing the anesthetic agent and tracheal extubation:

- 100 % O₂ is given by a face mask.
- Patient's airway is supported until respiratory reflexes are intact.
- The patient's muscle power and co-ordination are assessed e.g., testing handgrip, tongue protrusion, lifting unsupported head off the pillow in response to command.
- The patient should be placed in the recovery position to avoid aspiration especially for surgeries involving airway as tonsillectomy.

Post-operative Management

The responsibility of anesthesiologists does not end by a complete patient recovery from the effects of the anesthetics, but it continues till normal vital signs have been established and the patient's condition seems stable.

The patient is discharged from the operating room to the post-anesthetic care unit (PACU) (recovery room) in which the anesthesiologist should remain with the patient till being discharged from PACU.

Before discharge from PACU, a **discharge note** should be written by the anesthesiologist to document;

- The patient's recovery from anesthesia.
- Any apparent anesthesia-related complications and pain status and their management.
- The patient's immediate postoperative condition.
- The disposition i.e., discharge to
 - An outpatient area. - Inpatient ward. - Intensive care unit (ICU) - Home.
- Inpatients should be seen again at least once by the anesthesiologist within 48 hours after discharge from PACU.

Approach of Anesthetic Management

Definition and Pathophysiology (+ causes and clinical pictures)

Anesthetic Problems and Considerations:

I) Preoperative Management:

1- **Patient assessment:** (by history, examination, and investigations)

From clinical picture, other systems, drug therapy (side effects and interactions).

2- **Patient preparation:** (elective or emergency surgery)

3- **Premedications:** (sedatives, anticholinergics, \pm aspiration prophylaxis).

II) Intraoperative Management:

- **Monitoring**
- **Patient position** (technique, complications, and precautions)

• Choice of anesthesia

a- **Regional anesthesia** (advantages and disadvantages)

b- **General anesthesia** (advantages and disadvantages)

1- **Induction:** - Type of induction (smooth, crash,...etc)

- Induction agents

- Muscle relaxants

- Endotracheal intubation and the pressor response.

2- **Maintenance:** Balanced, inhalational-based, or opioid-based anesthesia.

$O_2 \pm N_2O$ + inhalational agents + opioids + muscle relaxants + mechanical ventilation

3- **Intraoperative problems** (causes and treatment)

4- **Fluid therapy** (amounts and types)

5- **Body temperature control.**

6- **Recovery and extubation** (awake or deep extubation)

(+ criteria of extubation and reversal of muscle relaxation).

III) Postoperative Management:

1- Patient's transfer is to the ward or intensive care unit (ICU) (indications).

2- Pain management (why and how?).

3- Postoperative care and close monitoring to detect complications (they are similar to intraoperative complications).

There is a Golden Rule during Anesthetic Management

There are **priorities of organ protection** during anesthetic management of the patient. These priorities are arranged from the most important to the less important (although all patients' organs are important):

- **Airway protection: (at first maintenance of ventilation, then protection against aspiration).**

- Brain protection.

- Myocardial protection.

- Respiratory protection.

- Renal and liver protection.

- Other organ protections e.g., eyes.

For example:

- A patient with a **full stomach** and suspected to have **difficult intubation or ventilation**, awake intubation is the best to protect the airway, but in case of uncooperative patient, child, or even patient's refusal, inhalational induction should be done to protect the airway against difficult intubation although there is still a risk of aspiration.

- A patient with a **full stomach**, with **elevated intracranial pressure**, the induction of anesthesia should be crash rapid sequence (or a modified crash induction by addition of fentanyl) to protect the airway first. After that, the protection is directed to the brain.

- A patient with advanced coronary artery disease who should have a **cardiac surgery**, but in the same time his **carotid artery is severely atherosclerotic** and needs surgery. This patient should be operated upon for carotid endarterectomy before coronary artery bypass grafting.

- A patient with a **full stomach** and with **traumatic eye injury**, induction of anesthesia should be done by crash rapid sequence induction (or a modified crash induction) to protect the airway at first. Protection of the eyes comes in the second place.

Evidence-Based Medicine (EBM)

Definition:

It is the conscientious, explicit, and judicious use of current best evidence in making decisions about the diagnosis, treatment, and care of individual patients.

Designation of Levels of Evidence:

- **Level I Conclusive:** reviews of meta-analyses i.e., large-scale randomized prospective controlled trials with clear results and low alpha or beta error.

- **Level II Strong:** small properly designed randomized controlled study with uncertain results with moderate to high alpha/beta error.

- **Level III Moderate:** non-randomized comparative studies with controls.

- **Level IV Limited:** well-designed non-experimental non-randomized studies with historical controls and expert opinion.

- **Level V Indeterminate:** Opinions of respected authorities or non-randomized uncontrolled studies.

A grading system may then be applied:

- **Grade A:** supported by at least 2 level I investigations.
- **Grade B:** supported by 1 level I investigations.
- **Grade C:** supported by level II investigations only.
- **Grade D:** supported by at least 1 level III investigations.
- **Grade E:** supported by level IV or V evidence.

The Relation between Individual Clinical Expertise (Experience-Based Medicine) and the External Clinical Evidence (Evidence-Based Medicine):

- There must be integration between **individual clinical expertise** (that is important in obtaining information during history, physical examination, and performance of appropriate tests) and the **best available external clinical evidence** (i.e., information obtained from medical literature) that is derived from systematic research.
- This integration is used to make a knowledge that is used in diagnosis and treatment.
- EBM gives less importance to intuition and more emphasis to a systematized approach to health care.
- This approach does not devalue individual clinical expertise, instead supplementing it.

Further Readings:

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Web Sites:

- <http://www.aagbi.org>
- <http://www.nice.org.uk>

PHARMACOLOGY OF ANESTHESIA & INTENSIVE CARE

- Definition of general anesthesia
- Theories of general anesthesia
- Inhalational anesthetic agents
- Intravenous anesthetic agents
- Opioid (narcotic) analgesics
- Benzodiazepines

- Neuroleptics
- Skeletal muscle relaxants
- Cholinesterase inhibitors (Anticholinesterases)
- Sugammadex
- Local anesthetics

Definition of General Anesthesia

It is an altered physiologic state in which, as a result of **reversible, drug-induced unconsciousness**, noxious stimuli can neither be perceived nor recalled.

Theories of General Anesthesia Action

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There are many theories, but none of them completely explains the mode of action of all anesthetics.

1- Lipid Solubility Theory (the Unitary Hypothesis):

- It was originally developed in 1901 by HH Meyer & E Overton.
- It suggested that all anesthetics have a common mechanism of action at the molecular level and act by this theory (hence, the name unitary). This theory is supported by the observation that, there is a correlation between anesthetic potency (minimal alveolar concentration "MAC") and lipid solubility (Oil/gas partition coefficient). This is called **Meyer Overton rule** as the anesthetic molecules bind at specific lipophilic sites.
- Objections against the theory: not all lipid-soluble molecules are anesthetics.

2. Aqueous Theory of Anesthetic Action (the Critical Volume Hypothesis):

- Anesthetics bind to hydrophobic sites in the phospholipid bilayer of the neuronal membrane. This expands the bilayer of the cell membrane beyond a critical volume that causes alteration in membrane function e.g., occluding its micro channels.
- Pressure reversal: It is noticed that increased pressure around laboratory animals results in:
 1. Reversal of anesthesia i.e., it allows anesthetized animals to wake up.
 - or 2. Resistance to anesthesia or a decrease in anesthetic potency.
- This is explained by: the increased pressure causes contraction of the expanded critical hydrophobic sites in the cell membrane which in turn causes displacement of a number of molecules from the membrane. This increases the anesthetic requirement.
- Objections against the theory: not all agents behave in the same way at high pressure e.g., some i.v. anesthetics.

3. The Fluidization Theory of Anesthesia:

Lipids in cell membranes move and rotate within the bilayer and influence the activity of proteins which control ionic and neurotransmitter fluxes. General anesthesia may increase the movement of lipid and increase its volume causing conformational changes in protein i.e., anesthetics fluidize lipids which make proteins relax into the inactive (closed-channel) state.

- Objections against the theory: not all anesthetic agents act in the same way.

4. Calcium Hypothesis:

- General anesthetics cause an increase in cytoplasmic Ca^{++} (increase resting free Ca^{++}) which:
 - activates Ca^{++} dependent K^{+} channels that results in hyper-polarization of the cell membrane, or/and - augments GABA_A receptor-mediated inhibition.
- Objections against the theory: it is still unclear as increased resting Ca^{++} is not a constant finding with volatile anesthetics in neurons.

Site of Action of General Anesthetics

At the Macroscopic Level

General anesthetic agents act on specific brain areas such as the reticular activating system, the cerebral cortex, the cuneate nucleus, the olfactory cortex, and the hippocampus.

At the Microscopic Level

Anesthetics are selective in their action at a cellular and molecular level, so unitary hypothesis is unlikely nowadays.

Neurotransmitters concerned with general anesthetic action are either:

- **Excitatory** neurotransmitters (**acetylcholine and glutamate**); their inhibition produces general anesthesia.
- **Inhibitory** neurotransmitters (**gamma aminobutyric acid "GABA" and glycine**); their potentiation produces general anesthesia.

Affection of synaptic transmission occurs by:

A) Presynaptic Mechanisms:

It was found that general anesthetics **decrease synaptic transmission** of excitatory neurotransmitters (**acetylcholine and glutamate**) rather than axonal impulse conduction. This occurs by:

1- Decreased Release of Excitatory Neurotransmitters:

- activation of presynaptic K⁺ channels or
- blocking of presynaptic Na⁺ channels e.g., volatile anesthetics and propofol, (but not thiopental).

2- Decreased Synthesis of Acetylcholine

By prevention of choline reuptake e.g., high % of volatile anesthetics.

3- Increased Reuptake of Excitatory Neurotransmitters

By stimulation of protein kinase C e.g., volatile anesthetics.

4- Increased Leak of Presynaptic Vesicles of Excitatory Neurotransmitters (Proton Pump Leak Theory)

This is done by decreasing pH gradients.

B) Postsynaptic Mechanisms:

Each anesthetic agent binds at a specific protein site of the receptor, and at a certain time during opening of the pores of the receptors.

1- Activation of GABA_A Receptor

By increasing Cl⁻ current and affinity of GABA to the receptors.

2- Activation of Glycine Receptors (α₁-Subunits)

This potentiates glycine transmission.

3- Inhibition (Blocking) of Nicotinic Acetylcholine Receptors

This decreases acetylcholine transmission.

4- Inhibition (Blocking) of Glutamate Receptors

By blocking N-methyl-D-aspartate (NMDA) receptors which are subtypes of glutamate receptors.

Recently anesthetics have been classified into 3 classes based on their preferential targets.

Class I: These anesthetics act almost exclusively on GABA_A receptors.

Examples: • **Etomidate:** acts only on β₃ subunit containing receptors.

- **Propofol:** acts on both β₂ and β₃ subunit containing receptors.

- **Benzodiazepines:** act only on γ subunits of GABA_A receptors.

Class II: These anesthetics act on GABA_A receptors and other sites such as:

- Activation of presynaptic potassium channels.
- Inhibition of presynaptic sodium channels.
- Activation of glycine receptors.
- Inhibition of nicotinic acetylcholine or glutamate receptors.

Examples: • **Barbiturates.**

• **Potent inhalational agents.**

• **Propofol.**

Class III: These anesthetics inactivate GABA_A receptors, but also affect other sites as blocking NMDA subtype of glutamate receptors.

Examples: • **Ketamine** (NMDA blocking effect is its main action).

- **Cyclopropane, N₂O, and xenon** (block both GABA_A and NMDA receptors).
- **Selective α₂ agonists as clonidine** (do not block NMDA receptors).

INHALATIONAL ANESTHETIC AGENTS

Pharmacokinetics of Inhalational Anesthetics

Pharmacokinetics is the effect of the body on a drug.

Inhalational Anesthetic Absorption and Distribution

Factors Affecting Inspiratory Fraction (F_i) or Concentration

- 1- Increasing fresh gas flow rate.
- 2- Decreasing volume of the breathing system.
- 3- Decreasing absorption by the breathing system.

These factors increase the inspired gas concentration to reach the same value of the fresh gas concentration. This produces faster induction (and recovery).

Factors Affecting Alveolar Fraction (F_A) or Concentration

1- Uptake:

• If there was no uptake of anesthetic agents by the body, the alveolar gas concentration (F_A) would rapidly approach the inspired gas concentration (F_i), but actually there is uptake of anesthetic agents by the body; therefore, the alveolar gas concentration will be less than the inspired gas concentration i.e., $F_A/F_i < 1.0$.

The greater the uptake of an anesthetic agent,

- the lower the rate of rise of the alveolar concentration,
- the greater the difference between inspired and alveolar concentrations,
- the slower the rate of induction and (also recovery).

Factors affecting anesthetic uptake:

1- Solubility in blood (blood/gas solubility coefficient):

• The higher the blood/gas solubility coefficient, the greater the anesthetic solubility in the blood; therefore, more soluble agents (e.g., halothane) must be dissolved in blood than insoluble agents (e.g., N_2O) to raise the partial pressure of blood until equilibrium is reached (i.e., before P_A equilibrates with the P_A). The blood is considered a pharmacologically inactive reservoir, the size of which is determined by the solubility of the anesthetic in the blood. This produces slower onset of induction and recovery with these soluble agents.

• Insoluble agents (e.g., N_2O) are taken up by the blood less avidly than soluble agents (e.g., halothane); therefore, the alveolar concentration (and alveolar partial pressure) of N_2O rises faster than that of halothane. This allows faster induction (and recovery) with these insoluble agents.

Therefore, the higher the blood/gas solubility coefficient, the greater the anesthetic solubility and the slower the onset of induction and recovery (figure 3-1).

Onset of induction and recovery $\propto \frac{1}{\text{Blood/gas solubility coefficient}}$

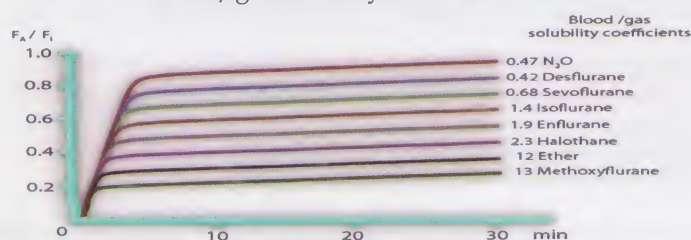


Figure 3-1: F_A rises toward F_i faster with N_2O than with methoxyflurane

2- Alveolar blood flow:

• Increased alveolar blood flow (in absence of pulmonary shunting) and increased cardiac output increase anesthetic uptake. This produces a slow rise of alveolar partial pressure (P_A) which in turn makes the onset of induction slow.

• This effect is more obvious with agents that are soluble in blood e.g., halothane.

3- Partial pressure difference between alveolar gas and venous blood ($P_A - P_V$):

If the anesthetics do not pass into organs (as brain), venous and alveolar partial pressures will become identical and there will be no pulmonary uptake, but actually, there is a transfer of anesthetics from blood to tissues, which is determined by 3 factors:

- Tissue solubility of the agent (tissue/blood partition coefficient).

- Tissue blood flow.
- Partial pressure difference between arterial blood and the tissue.

Tissues are classified into:

Type of Tissues	Cardiac Output (%)	Relative Solubility	Capacity
a. Vessel-rich group: brain, heart, liver, kidney and endocrine glands	75	1	Small capacity (they are the first to take up appreciable amounts of anesthetics and the first to fill)
b. Muscle group: skin and muscles	19	1	Greater capacity (due to their large volume, therefore the uptake is sustained for hours to fill)
c. Fat group	6	20	Greater capacity (the uptake is sustained for days to fill).
d. Vessel-poor group: bone, ligaments, teeth, hair and cartilages	0	0	Small capacity (there is insignificant uptake).

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2- The Rate of Delivery of the Anesthetic Agents to the Alveoli: depends on:

1- **Ventilation:** increased ventilation causes increased delivery of anesthetic agents to the alveoli which compensates for their uptake. This maintains alveolar concentration, which causes a more rapid onset of induction especially for soluble agents.

2. **Concentration:**

a- **Concentration effect:** increasing the concentration (by adjusting the vaporizer) leads to an increase in alveolar concentration and its rate of rise; therefore, shortens the induction time especially with insoluble agents e.g., N_2O .

N_2O is more soluble in blood than nitrogen so, the volume of N_2O entering pulmonary capillary blood from the alveoli is greater than the volume of nitrogen moving in the opposite direction; therefore, the total volume of gas in the alveoli decreases resulting in an increased fractional concentration of the N_2O itself. The higher the inspired concentration of N_2O , the greater the concentrating effect is.

b- **Second gas effect:** if 2 gases are given simultaneously e.g., N_2O and halothane, the large volume uptake of the first gas (N_2O) augments the rate of increase of the alveolar concentration of the 2nd gas (halothane) and also O_2 , so PaO_2 (the 2nd gas) is increased. This is called **alveolar hyperoxygenation**.

In other words, 2nd gas effect is the concentration effect of one gas upon the other.

C- Factors Affecting Arterial Concentration (Fa)

It is mainly affected by ventilation/perfusion (V/Q) mismatching.

Normally, alveolar and arterial anesthetic partial pressures are assumed to be equal. The presence of V/Q mismatching increases alveolar-arterial differences i.e., increases alveolar partial pressure (especially for highly soluble agents) and decreases arterial partial pressure (especially for poorly soluble agents).

Therefore, abnormal intubation or a right-to left intracardiac shunt will slow the rate of induction.

II) Inhalational Anesthetic Elimination and Metabolism

See later.

Pharmacodynamics of Inhalational Anesthetics

Pharmacodynamics is the effect of a drug on the body.

Minimum Alveolar Concentration (MAC)

Definition:

It is the minimum alveolar concentration of an anesthetic at 1 atmosphere absolute that prevents movement of 50% of the population to a standard stimulus (e.g., surgical incision).

Values of Measuring MAC:

- It allows **comparison of potency** between agents. Potency is defined classically in terms of MAC.
- It provides a **standard for experimental evaluation**.
- It is **roughly additive** (see MAC values later) e.g., a mixture of 0.5 MAC of N_2O (53%) and 0.5 MAC of halothane (0.37%) approximates the degree of central nervous depression of 1.0 MAC of isoflurane (1.15%).
- It **represents** only one point on the dose-response curve. It is the equivalent of a median effective dose or an **effective dose 50 (ED50)** (figure 3-2). From the figure, both drugs "A" and "B" are effective because they reach 95% response, but drug "A" is more potent than drug "B" because the former has less MAC_{50} and reaches the 95% at lower MAC_{95} . Drug "C" is less effective and less potent.

MAC has a limited value during managing and anesthetizing patients. It **does not represent the dose of inhalational anesthetic** as it produces anesthesia in 50% of patients only.

Types of MAC:

1- **MAC₅₀**: as above.

2- **MAC awake**: it is the minimal alveolar concentration **allowing voluntary response** to command in 50% of patients (e.g., open your eyes). It is 0.3-0.4 times MAC i.e., 30-40% of MAC for isoflurane, desflurane, and sevoflurane and it is 0.7 times MAC for N₂O.

3- **MAC_{95%}**: it is the MAC that prevents movement in about 95% of patients (an approximation of the ED₉₅). It **represents the dose of inhalational anesthetics**.

It is 1.3 times MAC of any of the volatile anesthetics.

4- **MAC intubation**: it is the MAC that **allows intubation** without a muscle relaxant, coughing, or bucking in 50% of patients.

5- **MAC BAR**: it is the MAC that **Blocks the Adrenergic Response** to intubation and incision.

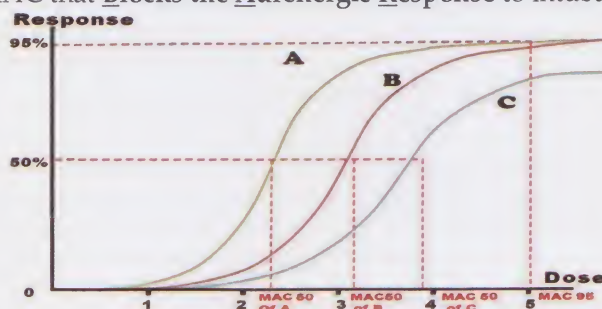


Figure 3-2: A dose-response curve

Factors Affecting MAC:

Factors Decreasing MAC (Central Nervous System Depression)	Factors Increasing MAC (Central Nervous System Excitation)
1- Hypothermia and hyperthermia 2- Age: elderly (there is a 6% decrease in MAC per decade of age) 3- Alcohol: acute toxicity 4- Myxoedema (some authors deny this) 5- Hyponatremia 6- Others as - anemia (< 5g %) - hypotension (mean blood pressure < 40mmHg) - Hypoxia (PaO ₂ < 40mmHg) - Hypercapnia (PaCO ₂ > 95mmHg) 7- Drugs: • Sympatholytics: methyl dopa, reserpine, clonidine, and dexmedetomidine. • Chronic amphetamine abuse. • Local anesthetics (except cocaine) • Others: N ₂ O, barbiturates, ketamine, opioids, propofol, benzodiazepines, etomidate, verapamil, and lithium.	1- Hyperthermia > 42°C 2- Young (MAC is highest at age 6 months) 3- Chronic alcohol abuse. 4- Thyrotoxicosis (some authors deny this) 5- Hypernatremia 6- Others as - patients with red hair. 7- Drugs: • Sympathomimetics: cocaine, and ephedrine. • Acute amphetamine toxicity. • Cocaine.

Types Inhalational Anesthetics

a- **Inert Elements**: Xenon.

b- **Inorganic Compounds**: Nitrous Oxide (N₂O; laughing gas).

c- **Organic Compounds**:

• **Halogenated hydrocarbons** (halogenated alkane): (R – R)

Example: **Halothane**: 2-bromo-2-chloro-1,1,1-trifluoroethane.

• **Halogenated ethers** (R – O – R)

Examples: - **Diethyl ether** (*Ether*).

- **Methoxyflurane**: halogenated methyl ethyl ether.

- **Isoflurane**: 1-chloro-2,2,2-trifluoroethyl difluoro-methyl ether.


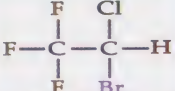
- **Enflurane**: it is an isomer of isoflurane.

- **Desflurane**: it is similar to isoflurane, but a fluorine atom is present instead of a chlorine atom.

- **Sevoflurane**: fluoromethyl-2,2,2-trifluoro-1-ethyl ether.

Q: Classify inhalational anesthetic agents according to their chemical structures?

Inhalational Anesthetics Still Used in the Clinical Practice:

	Nitrous Oxide (N ₂ O)	Halothane (Fluothane)
Chemical structure	Inorganic 	Organic, halogenated hydrocarbon 
Physical values • Molecular weight in Dalton (MW) • Saturated vapor pressure at 20 °C in kilopascal (SVP) • Saturated vapor concentration at 20 °C in % (SVC) • Boiling point in °C (BP).	<ul style="list-style-type: none"> • MW: 44 • SVP: 5300 • BP: - 88 • Critical temperature (°C): 36.5 • Critical pressure (bar): 72.6 <p>N.B.: 1 kPa = 7.6 mmHg = 0.01 bar</p>	<ul style="list-style-type: none"> • MW: 197 • SVP: 32 • SVC: 32 • BP: 50.2 <p>N.B.: Both halothane and isoflurane have nearly the same SVP, therefore; theoretically they can be used by the same vaporizer.</p>
Physical properties	<ul style="list-style-type: none"> • Non-flammable and non-explosive but supports combustion (as O₂). • Colorless and odorless. • Stable. • Stored as a liquid in a blue cylinder at pressure 47-50 bar. Its total quantity is assessed by weighing. 	<ul style="list-style-type: none"> • Non-flammable and non-explosive (due to carbon-fluoride bonds). • Colorless and relative pleasant odor. • Decomposed by light, heat and soda lime (but used safely with soda lime). • Stored in opaque bottles with 0.01% thymol as a preservative. It may cause acute lung injury, therefore; it is recommended to evacuate the vaporizer every 2-3 weeks completely.
MAC and onset	<ul style="list-style-type: none"> • MAC = 105 % (hyperbaric condition is needed). • Fastest induction and fastest recovery because it has the lowest blood/gas coefficient =0.47 	<ul style="list-style-type: none"> • MAC = 0.75% • Relatively rapid induction (less than enflurane and isoflurane) as it has a relatively low blood/gas coefficient 2.3
Excretion and metabolism (rule of 2)	<ul style="list-style-type: none"> • The main route of excretion of all anesthetic agents is the lungs. Minimal excretion occurs via the skin by evaporation. • Metabolism occurs in the liver by cytochrome P-450 isoenzymes (specifically CYP2E1). 	<ul style="list-style-type: none"> • 20% are metabolized by oxidative pathways to bromine, chlorine, trifluoro-acetic acid and tri-fluoro-acetyl ethanol amide. They are excreted in the urine. • A small % by reductive pathways (i.e., in absence of O₂) to reactive metabolites and fluoride (in concentrations lower than those which induce renal dysfunction). It occurs in presence of hypoxia, or phenobarbitone which causes hepatic microsomal enzyme induction.
Toxicity Q: What are the precautions of prolonged anesthesia?	<p>.....</p> <p>Toxicity: On prolonged exposure > 6-8 hours</p> <p>1- It irreversibly oxidizes the cobalt atom in vitamin B₁₂ which causes inhibition of vitamin B₁₂ dependent enzymes as:</p> <ul style="list-style-type: none"> • Methionine synthetase → impairment of myeline synthesis → neurological deficiencies as peripheral neuritis and myelo-neuropathy • Thymidylate synthetase → impairment of DNA synthesis → megaloblastic anemia, agranulocytosis, bone marrow aplasia. <p>2- It has a possible teratogenic effect, so it should be avoided in early pregnancy.</p> <p>3- It changes the immune response to infection by affecting chemotaxis and white blood cell motility.</p>	<p>.....</p> <p>Toxicity: Halothane hepatitis</p>

Isoflurane (Forane)	Desflurane (Suprane)	Sevoflurane (SEVOflurane or Ultane)
Organic, ether $\begin{array}{c} \text{F} & & \text{H} & \text{F} \\ & & & \\ \text{H}-\text{C}-\text{O}-\text{C}-\text{C}-\text{F} \\ & & & \\ \text{F} & & \text{Cl} & \text{F} \end{array}$	Organic, ether $\begin{array}{c} \text{F} & & \text{H} & \text{F} \\ & & & \\ \text{H}-\text{C}-\text{O}-\text{C}-\text{C}-\text{F} \\ & & & \\ \text{F} & & \text{F} & \text{F} \end{array}$	Organic, ether $\begin{array}{c} & & \text{F} \\ & & \\ \text{F} & \text{F} & \text{C}-\text{F} \\ & & \\ \text{H}-\text{C}-\text{O}-\text{C} \\ & & \\ \text{H} & \text{F} & \text{C}-\text{F} \\ & & \\ & & \text{F} \end{array}$
<ul style="list-style-type: none"> • MW: 184.5 • SVP: 32 • SVC: 32 • BP: 48.5 	<ul style="list-style-type: none"> • MW: 168 • SVP: 88 • SVC: 88 • BP: 22.8 <p>N.B.: Because its BP is near room temperature and its SVP is near 100 kPa; therefore, it needs a special vaporizer (Tec 6)</p>	<ul style="list-style-type: none"> • MW: 200 • SVP: 21 • SVC: 21 • BP: 58.6
<ul style="list-style-type: none"> • Non-flammable and non-explosive • Colorless and pungent odor. • Stable with soda lime but carbon monoxide may be formed. • Stored in opaque bottles with no preservative. 	<ul style="list-style-type: none"> • Non-flammable and non-explosive. • Colorless and much less pungent odor. • Stable with soda lime but carbon monoxide may be formed. • Stored in opaque bottles with no preservative. 	<ul style="list-style-type: none"> • Non-flammable and non-explosive. • Colorless and pleasant odor • Decomposed by soda lime if low fresh gas rates are used (see toxicity) and compound A is formed. • Stored in opaque bottles with no preservative
<ul style="list-style-type: none"> • MAC = 1.15% • Rapid induction (but limited) and more rapid recovery as it has a low blood/gas coefficient 1.4 <p>Its pungent odor causes coughing and breath-holding, so clinically it is not more than halothane.</p>	<ul style="list-style-type: none"> • MAC = 6-9 (7.3) • The most rapid induction (but limited) and the most rapid recovery as it has a very low blood/gas coefficient 0.42 <p>Pungent odor is irritant, so it is avoided in children.</p>	<ul style="list-style-type: none"> • MAC = 2.0% • Rapid induction as it has a low blood/gas coefficient 0.68 and it is not irritant. It has slower recovery (than desflurane). <p>N.B.: Due to this rapid induction, sevoflurane can be used for induction of anesthesia in adults easily, therefore the term VIMA is present (it is volatile induction and maintenance of anesthesia).</p>
<ul style="list-style-type: none"> • The main route of excretion of all anesthetic agents is the lungs. Minimal excretion occurs via the skin by evaporation. • Metabolism occurs in the liver by cytochrome P-450 isoenzymes (specifically CYP2E1). 		
<ul style="list-style-type: none"> • 0.2% is metabolized by oxidative pathways to trifluoroacetic acid and difluoro methanol which produces formic acid and fluoride. <p>-----</p> <p>Toxicity:</p> <ul style="list-style-type: none"> • Hepatotoxicity: Extremely rare (isoflurane < enflurane < halothane) 2. Nephrotoxicity: Fluoride level does not reach the renal toxic level. 	<ul style="list-style-type: none"> • 0.02 % is metabolized by oxidative pathways to trifluoroacetic acid and very little fluoride. <p>-----</p> <p>Toxicity:</p> <p>No evidence of hepatic or renal toxicity.</p>	<ul style="list-style-type: none"> • 2% are metabolized by oxidative pathways to inorganic fluoride (> Isoflurane) that may affect the kidney and organic fluoride (hexafluoro-isopropanol) that conjugate rapidly in the liver with glucuronic acid, which is then excreted in urine. Although organic fluoride is hepatotoxic, its rapid conjugation and excretion decrease the risk of liver damage. <p>-----</p> <p>Toxicity:</p> <ul style="list-style-type: none"> • Hepatotoxicity Very rare. • Nephrotoxicity It is better avoided in patients with renal impairment if low fresh gas flow rates are used due to fluoride and compound "A" or olefin (see later).

	Nitrous Oxide (N ₂ O)	Halothane (Fluothane)
Actions		
1- Neuro-logical effects	<ul style="list-style-type: none"> • All agents are good anesthetics and weak analgesics except N₂O which is a good analgesic and a weak anesthetic. • All agents produce cerebral vaso-dilatation and impair auto-regulation. Both increase cerebral blood flow and intra-cranial tension (ICT). • All agents produce a dose dependent depression of electroencephalography (EEG) with burst suppression (enflurane may also cause paroxysmal epileptic-form activity) except N₂O which causes unusual activation. • All agents decrease cerebral metabolic rate of O₂ consumption (CMRO₂) except N₂O which increases it due to its unusual cerebral activation. • All agents cause emergence agitation (i.e., excitation on awakening) except N₂O. 	<ul style="list-style-type: none"> • It mildly increases ICT as before. • It increases ICT more than other agents.
2- Respiratory effects	<ul style="list-style-type: none"> • All agents produce respiratory depression and cause an increase in the respiratory rate (RR) with a decrease in the tidal volume (V_t) i.e. rapid shallow breathing; therefore, minute ventilation is decreased and resting PaCO₂ is increased (Enflurane > desflurane > isoflurane > halothane > sevoflurane > N₂O). • All agents depress the hypoxic drive and the ventilatory response to hypercapnia. • All agents produce bronchodilatation except N₂O. 	<ul style="list-style-type: none"> • It is not irritant to the respiratory tract. • It is a potent bronchodilator due to its central effect, β action, and inhibition of intracellular Ca⁺⁺ mobilization. • It causes retention of secretions because it depresses mucociliary function for hours postoperatively.
3- Cardio-vascular effects	<ul style="list-style-type: none"> • It has a dual action on the heart (like ketamine): <ul style="list-style-type: none"> a- Direct action depresses the heart. b- Indirect action via stimulation of the sympatho-adrenal system that stimulates catecholamine release and may produce arrhythmias. The indirect action overcomes the direct action; therefore, cardiac depression is not apparent. If the sympatho-adrenal system is exhausted (as in severe prolonged heart failure or severe end-stage shock) or depressed by opioids or β blockers, depression of the heart becomes apparent and reduction of blood pressure, cardiac output, and heart rate occurs. • It produces vasoconstriction of pulmonary vessels and increases pulmonary vascular resistance. 	<ul style="list-style-type: none"> • Cardiac output and contractility: all agents (except N₂O) depress them in a dose dependent manner. This action may increase the right atrial pressure (halothane > enflurane > isoflurane > desflurane > sevoflurane). • Arterial blood pressure and systemic vascular resistance: all agents (except N₂O) decrease them by producing vasodilatation (isoflurane > desflurane > sevoflurane > halothane > enflurane). • Anesthetic preconditioning: all agents have a protective effect on the heart, limiting the area of myocardial injury, preserving function after exposure to an ischemic insult (such as a period of hypoxia) i.e., ischemic preconditioning e.g., inhalation of 0.2-1 MAC, during the entire coronary artery bypass grafting surgery, decreases the risk of infarction. This occurs by opening of mitochondrial ATP-sensitive K⁺ channels (K_{ATP}). • Heart rate: is reduced due to: <ul style="list-style-type: none"> - Central vagal stimulation. - Abolishment of the baroreceptor reflex that occurs with hypotension. This is antagonized by atropine. • Arrhythmias: are common due to: <ul style="list-style-type: none"> - increased sensitization of myocardium to the circulating catecholamines (this also occurs slightly with enflurane) especially with hypoxia and hypercapnia. - central vagal stimulation (bradycardia and junctional nodal rhythm). • It reduces coronary blood flow, but due to the reduced contractility and heart rate, there is reduced O₂ demand, so halothane is used safely in ischemic heart patients.

Isoflurane (<i>Forane</i>)	Desflurane (<i>Suprane</i>)	Sevoflurane (<i>SEVOflurane</i>)
<ul style="list-style-type: none"> All agents are good anesthetics and weak analgesics except N₂O which is a good analgesic and a weak anesthetic. All agents produce cerebral vaso-dilatation and impair auto-regulation. Both increase cerebral blood flow and intra-cranial tension (ICT). All agents produce a dose dependent depression of electroencephalography (EEG) with burst suppression (enflurane may also cause paroxysmal epileptic-form activity) except N₂O which causes unusual activation. All agents decrease cerebral metabolic rate of O₂ consumption (CMRO₂) except N₂O which increases it due to its unusual cerebral activation. All agents cause emergence agitation (i.e., excitation on awakening) except N₂O. 		
<ul style="list-style-type: none"> It increases ICT only at high levels (>1 MAC). EEG: it produces an isoelectric line at high levels (> 2 MAC). 	<ul style="list-style-type: none"> It increases ICT only at high levels (>1 MAC). EEG: it produces an isoelectric line at high levels (> 2 MAC). 	<ul style="list-style-type: none"> It slightly increases ICT. It produces emergence agitation more than other agents (treated by fentanyl 1-2 µg/kg).
<ul style="list-style-type: none"> All agents produce respiratory depression and cause an increase in the respiratory rate (RR) with a decrease in the tidal volume (V_t) i.e., rapid shallow breathing; therefore, minute ventilation is decreased and resting PaCO₂ is increased (Enflurane > desflurane > isoflurane > halothane > sevoflurane > N₂O). All agents depress the hypoxic drive and the ventilatory response to hypercapnia. All agents produce bronchodilatation except N₂O. 		
<ul style="list-style-type: none"> It is irritant to the respiratory tract; therefore, coughing, breath-holding and profuse secretions from the salivary and bronchial glands occur. 	<ul style="list-style-type: none"> It is irritant to the respiratory tract..... 	<ul style="list-style-type: none"> It is not irritant to respiratory tract. It is the least one affecting the respiration.
<ul style="list-style-type: none"> Cardiac output and contractility: all agents (except N₂O) depress them in a dose dependent manner. This action may increase the right atrial pressure (halothane > enflurane > isoflurane > desflurane > sevoflurane). Arterial blood pressure and systemic vascular resistance: all agents (except N₂O) decrease them by producing vasodilatation (isoflurane > desflurane > sevoflurane > halothane > enflurane). Anesthetic preconditioning: all agents have a protective effect on the heart, limiting the area of myocardial injury, preserving function after exposure to an ischemic insult (such as a period of hypoxia) i.e., ischemic preconditioning e.g., inhalation of 0.2-1 MAC, during the entire coronary artery bypass grafting surgery, decreases the risk of infarction. This occurs by opening of mitochondrial ATP-sensitive K⁺ channels (K_{ATP}). Volatile agents improve the balance of O₂ supply and demand in the myocardium by dilating coronary arteries, preserving energy-dependent cellular function, and attenuating the action of reactive O₂ species (O₂ free radicals) which have been implicated in myocardial ischemic injury. 		
<ul style="list-style-type: none"> Heart rate: is increased because it does not blunt the baroreceptor reflex. Arrhythmias are uncommon It increases coronary blood flow due to vasodilatation, but there is a possibility of coronary steal phenomenon where the vasodilatation occurs in the normal coronary artery and not in the stenosed vessels. This decreases perfusion to the ischemic areas. Therefore, it is controversial in patients with coronary disease. 	<ul style="list-style-type: none"> Heart rate: is increased because it does not blunt the baro-receptor reflex. Arrhythmias are uncommon. Cardiac output is maintained because the depression of contractility and the reduction of blood pressure are antagonized by the increased heart rate. 	<ul style="list-style-type: none"> Heart rate: is increased because it does not blunt the baro-receptor reflex. Arrhythmias are uncommon. Cardiac output is maintained because the depression of contractility and the reduction of blood pressure are antagonized by the increased heart rate.

	Nitrous Oxide (N ₂ O)	Halothane (Fluothane)	Isoflurane (Forane)	Desflurane (Suprane)	Sevoflurane (SEVOflurane)
4- Neuro-muscular effects	<ul style="list-style-type: none"> All agents relax skeletal muscles and potentiate muscle relaxants by variable degrees. All agents are triggering to malignant hyperthermia (except N₂O). They cause postoperative shivering which increases O₂ requirement and produces hypoxia unless O₂ is given. 				
	Minimal	Moderate	Significant	Significant	Significant
5- Renal effects	All agents decrease renal blood flow which in turn decreases glomerular filtration rate and urine output due to reduction of blood pressure and cardiac output.				
6- Hepatic effects	All agents decrease the hepatic blood flow (due to reduction of blood pressure and cardiac output) except sevoflurane which may increase it (due to hepatic artery vasodilatation).				
7- Other effects	<ul style="list-style-type: none"> It causes postoperative nausea and vomiting due to stimulation of the chemoreceptor trigger zone and vomiting center in the medulla. All agents except N₂O decrease gastrointestinal motility. All agents except N₂O relax the uterus in a dose dependent manner, especially in therapeutic abortion (because the uterus is not yet well developed), which leads to increased blood loss, but in cesarean section, the relaxing effect is minimal, especially at a low concentration (because the uterus is well developed). 				
Contra-indication	<p>1- Effect on closed gas spaces: as N₂O is 35 times more soluble than nitrogen in blood, thus it tends to diffuse into air-containing cavities more rapidly than nitrogen is absorbed by the blood stream. This increases the volume of closed compliant space and the tension of the closed non-compliant space. Therefore, it is contraindicated in air embolism, acute intestinal obstruction, pneumothorax, pulmonary air cyst, intraocular air bubbles, tympanic membrane grafting. N₂O also diffuses into cuffs of endotracheal tubes and increases its pressure against the tracheal wall.</p> <p>2- Pulmonary hypertension: as it increases pulmonary vascular resistance.</p>				
	<p>1- Patients with liver or renal impairment according to the inhalational anesthetic agent.</p> <p>2- Patients with increased ICT.</p> <p>3- Patients with epilepsy especially with enflurane.</p> <p>4- Hypovolemic patients or those with impending heart failure.</p> <p>5- Patients with pheochromocytoma especially with halothane.</p> <p>6- Patients susceptible to malignant hyperthermia.</p>				
Drug interaction	<p>1- Concentration effect and 2nd gas effects are discussed above.</p> <p>2- Diffusion hypoxia: At the end of anesthesia, when inspired gas mixture is changed from N₂O/O₂ to N₂/O₂ so, the volume of N₂O diffusing from mixed venous blood into the alveolus is greater than the volume of nitrogen taken up from the alveolus into pulmonary capillary blood (the opposite of the concentration effect). Thus the concentration of gases in the alveoli is diluted by N₂O. This results in reduced PaO₂ (i.e., hypoxia) and PaCO₂. In healthy individuals, diffusion hypoxia is transient and may last up to 10 minutes. At the end of anesthesia, PaO₂ may decrease 5-10 mmHg so, postoperative 100% O₂ is essential.</p>	<p>1. Adrenaline containing local anesthetic solutions as arrhythmias occur, so</p> <ul style="list-style-type: none"> Avoid hypoxemia and hypercapnia. Avoid adrenaline concentration > 1: 200 000 Avoid dosages in adults > 10 ml of 1: 100 000 in 10 min or 30 ml/hr. <p>2. β blockers and Ca⁺⁺ channel blockers as increased myocardial depression occurs</p> <p>3. Aminophylline as serious ventricular arrhythmias occurs.</p>	<p>All agents potentiate non-depolarizing muscle relaxants.</p> <p>N.B.: Sevoflurane stabilization by water: Stored sevoflurane may rarely spontaneously degrade in the bottle or by metal and environmental impurities, present in manufacturing equipment, to volatile, highly acidic compounds "hydrogen fluoride". It can produce an acid burn on contact with respiratory mucosa. This degradation is reduced by adding water to sevoflurane during the manufacturing process and packaging it in a special plastic container. Bottles containing the degraded sevoflurane are under pressure (a hiss occurs on opening the bottle) and the gas coming from the bottle has an acrid odor.</p> <p>Q: What are the properties of an ideal inhalational anesthetic agent?</p> <p>A: The ideal properties can be estimated from the previous table e.g., it does not need a special vaporizer, non-flammable, non-explosive...etc.</p>		

Other Agents Rarely Used Nowadays

Enflurane

It has the following different characteristics:

- It is an **isomer to isoflurane**.
- Its **MAC is 1.68%**
- Hepato- and nephrotoxicity are very rare.
- It produces dose dependent depression of EEG up to burst suppression, but at moderate to high concentrations, **epileptic-form paroxysmal spike activity** occurs with twitches of the face and arm; therefore, it is contraindicated in epileptic patients.
- It is the **worst agent** as regard to **respiratory depression**.

Diethyl Ether (Ether)

It has the following different characteristics:

- It is highly **flammable and explosive**.
- Its **MAC is 1.9%**.
- It has a **very slow induction and recovery** because it has high blood/gas partition coefficient (12) therefore all the classical stages of anesthesia can obviously be seen.
- It has a much **higher therapeutic ratio** than halothane, enflurane, or isoflurane, so it is **safer to use** by unskilled individuals or from un-calibrated vaporizers.
- It can be administered by - an un-calibrated vaporizer (Boyle's bottle).
 - a calibrated vaporizer (EMO) as drawover or plenum vaporizers
 - a closed circuit with soda lime,
 - or - Schimmelbusch mask.

Methoxyflurane

It has the following different characteristics:

- Its **MAC is 0.2%** (the most potent).
- It is **highly metabolized in the liver (45-50%)** by oxidative pathways with production of high amounts of **free fluoride** and oxalic acid. Therefore, **nephrotoxicity** is common as the fluoride ions exceed the renal toxic threshold, resulting in:
 - Vasopressin-resistant high-output renal failure "**nephrogenic diabetes insipidus**" which is diagnostic of methoxyflurane toxicity).
 - Direct inhibition of tubular function with concentration defects.

Xenon

Xenon (Xe) is a Greek word for stronger. It is one of the noble gases (they are elements whose outer shells are filled with electrons). Nobel gases include xenon, helium, neon, argon, krypton, and radon.

Physical Properties:

- 1- Colorless, odorless, and tasteless gas.
- 2- Denser than air by 4 times.
- 3- Non-flammable and does not support combustion.
- 4- **Blood/gas partition coefficient** is extremely low **0.14**; therefore, it produces very rapid induction and recovery.
- 5- **MAC is 71 %** (i.e., with low potency).
- 6- Inert (probably nontoxic with no metabolism).

Metabolism and Elimination:

Are mainly through the lung.

Action:

1- Neurological effects:

- It produces cerebral depression; therefore, it can be used as an anesthetic and analgesic.
- It increases cerebral blood flow which in turn **increases intracranial tension**; therefore, cerebral perfusion pressure is decreased, so it is not recommended for neurosurgical procedures.

2- Respiratory effects:

- It decreases the respiratory rate (up to apnea) and increases the tidal volume (V_t); therefore, little change in the minute ventilation occurs.
- It has **higher density and viscosity** than N_2O , so it increases airway resistance during inhalation especially in patients with obstructive pulmonary diseases.

• Diffusion hypoxia is uncommon because xenon has a blood/gas partition coefficient much lower than that of nitrogen, so it diffuses through alveoli more slowly than N_2O .

3- Cardiovascular effects:

- **No significant change** occurs on contractility. It attenuates the myocardial depression effect of isoflurane causing preservation of myocardial performance.
- The heart rate is decreased because it stimulates the vagal action.

4- Neuromuscular effect:

- It does not trigger malignant hyperthermia.

5- Renal effects:

- It increases renal blood flow.

Uses:

1- As an anesthetic agent.

2- On measuring of cerebral blood flow (CBF) by inhalational methods,

For example: - to monitor cerebral blood flow in patients with severe head injury.

- to monitor cerebral perfusion during anesthesia.

3- In magnetic resonance imaging (MRI) as a contrast media.

4- Non-medical uses as laser, space study, and high potency lamps.

Advantages:

It is nearly an ideal anesthetic gas because of the following:

1- **Good physical properties** as colorless, odorless, tasteless, nonflammable, inert, and rapid induction and recovery.

2- **Action:** • It produces sufficient analgesia and hypnotic effect in a mixture with 30 % O_2 .

- It does not depress respiration markedly.
- It is the most cardio-stable anesthetic agent.
- It does not trigger malignant hyperthermia.

3- It is **environmentally friendly**.

Disadvantages:

1- It is **expensive**.

2- It has low potency.

3- It must be applied via a re-breathing system, but there is no commercially available anesthetic equipment.

4- It is not recommended for neurosurgery due to the increased ICT.

5- Due to its high density:

- it may change the accuracy of certain respiratory flowmeters.
- it increases airway resistance during inhalation especially in patients with obstructive pulmonary diseases.

A List for All Inhalational Anesthetics Used in Clinical Practice:

They are arranged from the oldest to the newest. Agents from 3-12 are obsolete.

1- N_2O .

2- Diethyl ether (ether).

3- Chloroform.

4- Ethyl chloride.

5- Ethylene.

6- Divinyl ether.

7- Cyclopropane.

8- Trichloroethylene.

9- Isopropenyl vinyl ether.

10- Propyl methyl ether.

11- Fluroxene.

12- Ethyl vinyl ether.

13- Halothane.

14- Methoxyflurane.

15- Enflurane.

16- Isoflurane.

17- Desflurane.

18- Sevoflurane.

Q: What does MAC represent in anesthesia?

A: • MAC = Minimal Alveolar Concentration (as above).

- MAC = Monitor Anesthesia Care e.g., during regional anesthesia of the eye, monitoring of critically ill patients doing procedures without anesthesia.

- MAC = Membrane Attack Complex. It is the terminal component of the complement cascade. It causes tissue, cellular, and microbial injury and produces multiple organ dysfunction syndrome.

Inhalational Anesthetic Toxicity

I- N₂O Toxicity

It is discussed above.

II. Hepatotoxicity

It occurs especially with halothane, but it is very rare with other agents such as methoxyflurane, enflurane, isoflurane, and sevoflurane. It is rare in pediatric patients.

Risk Factors:

- Middle age
- Obesity
- Female sex
- Positive family history.
- Re-exposure within 28 days.

Volatile agents (**halothane, isoflurane, desflurane, and enflurane**) are metabolized in the liver producing **trifluoroacetic acid (TFA)** which is harmful to the liver. **Sevoflurane** is metabolized in the liver producing **hexa-fluoro-isopropanol (HFIP)** instead of trifluoroacetic acid. HFIP is not toxic to the liver as it is conjugated with glucuronic acid in the liver and excreted by the kidney.

Types:

Type I	Type II (Halothane Hepatitis)
<ul style="list-style-type: none"> • It is more common. • It is also reported with enflurane and to a lesser extent isoflurane. • Clinical picture: (mild) <p>Mild changes in the liver function tests, which are transient and resolve within a few days.</p> <ul style="list-style-type: none"> • Mechanism: <p>Due to the reductive metabolism of halothane in the liver, there is increased glutathione-transferase concentration which reacts with hepatic macromolecules causing centri-lobular tissue necrosis. It is worsened by hypoxia.</p>	<ul style="list-style-type: none"> • It is extremely rare. • Its possibility increases on repeated exposure to the drug by 20%. • Clinical picture: (severe) <p>Severe jaundice up to fulminating hepatic necrosis, which causes high mortality (50%)</p> <ul style="list-style-type: none"> • Mechanism: (immune-mediated) <p>Due to the oxidative metabolism of volatile agents (except sevoflurane), trifluoroacetic acid is produced that binds covalently to hepatocyte proteins. This forms trifluoroacetyl-hepatocyte complexes that act as haptens (antigens) which the body recognizes as foreign bodies and to which the immune system forms antibodies. These antibodies are isolated. Subsequent exposure to any agent capable of producing trifluoroacetic acid may provoke an immune response against hepatocytes. Compound A of sevoflurane may affect the liver in the same manner.</p>

The Committee on Safety of Medicine Made the Following Recommendations:

1. A careful anesthetic history is taken to determine the previous exposure and any previous reactions to halothane.
2. Repeated exposure to halothane within a period of 3 months should be avoided unless there are overriding clinical circumstances.
3. A history of unexplained jaundice or pyrexia after previous exposure to halothane is an absolute contraindication to its future use in the same patient.

III. Nephrotoxicity

It can occur with methoxyflurane, enflurane, isoflurane, and sevoflurane. Theories of nephrotoxicity:

1. Traditional (Classical) Fluoride Hypothesis:

It suggests that anesthetics are metabolized in the liver producing inorganic fluoride. When the inorganic fluoride peak concentration reaches

- > 50 $\mu\text{mol/L}$ (**toxic fluoride threshold**), sub-clinical renal dysfunction occurs.
- > 80 $\mu\text{mol/L}$, clinical renal dysfunction occurs.

This hypothesis is suitable for **methoxyflurane** toxicity as it is very soluble; therefore, it continues to be metabolized for some days. This causes prolonged production of fluoride ions, but the peak fluoride concentration alone can not explain nephrotoxicity of sevoflurane as it does not produce renal dysfunction although its fluoride peak concentration is > 50 $\mu\text{mol/L}$.

2. Modified Fluoride Hypothesis:

It suggests that the **duration** of the plasma fluoride elevation, not just the peak concentration, determines nephrotoxicity.

This hypothesis is suitable for **enflurane** toxicity as prolonged enflurane anesthesia causes renal dysfunction, but prolonged sevoflurane or isoflurane does not produce renal dysfunction.

3. Renal Anesthetic Metabolism Hypothesis:

It states that **intra-renal metabolism** of anesthetics to fluoride or any other toxic metabolite is the cause of nephrotoxicity.

Intra-renal metabolism occurs by multiple cytochrome-P450 (CYP) enzymes. Methoxyflurane is more metabolized to fluoride in the kidney (by CYP2A6, CYP3A, and CYP2E1) than sevoflurane and enflurane (both are metabolized only by CYP2E1). This explains the high risk nephrotoxicity with methoxyflurane anesthesia. Nowadays, this is **the most accepted theory for all inhalational anesthetics**.

IV. Volatile Anesthetic Interaction with CO₂ Absorbents

The heat (60°C) and strong alkalinity of soda lime and baralyme can decompose volatile anesthetics producing toxic by-products.

Factors that Increase the Level of Toxic By-Products:

- 1- **Low fresh gas flow (FGF)** rates less than 1 L/min (especially with haloalkane toxicity).
- 2- The **dryness of the absorbent** (especially with carbon monoxide toxicity).
- 3- **Increased CO₂ absorbent temperature**.
- 4- **High anesthetic concentrations**.
- 5- **Increased CO₂ production** by the patients.
- 6- The use of **baralyme more** than soda lime.
- 7- **Prolonged time of exposure**.

Mechanism of Production of Toxic By-Products:

There are two types of toxic products produced:

a) Haloalkane: (with halothane and sevoflurane).

- **In animals (as rats)**, halothane and sevoflurane react with soda lime and baralyme producing toxic haloalkane compounds.
- Halothane is decomposed to haloalkane 2-bromo-2-chloro-1,1-difluoro ethane (BCDFE) compound.
- **Sevoflurane** is decomposed to fluoromethyl-2,2-difluoro-1-(tri-fluoro-methyl) vinyl ether which is known as "**compound A**" or "**Olefin**".

Both compounds are metabolized in the **liver** $\xrightarrow{\text{to}}$ **cysteine conjugates** which are metabolized in the **kidney** by a β -lyase enzyme $\xrightarrow{\text{giving}}$ **nephrotoxins** that cause proximal tubular necrosis.

- **In Humans**, the β -lyase activity is only 10% that in the kidney of rats, and so, the levels of haloalkane in humans are very low, and no halothane or sevoflurane nephrotoxicity is seen in humans.

For sevoflurane, some studies are still controversial; therefore,

Food and Drug Administration (FDA) recommends:

- 1- Avoiding the use of sevoflurane in patients with renal dysfunction especially at low fresh gas flow rates < 1 L/min.
- 2- Exposure to sevoflurane should not exceed 2 MAC-hour (i.e., exposure for one MAC for 2 hours) at < 1-2 L/min.

b) Carbon Monoxide: (with desflurane, enflurane or isoflurane).

- Desflurane, enflurane, and isoflurane (not halothane or sevoflurane) react with soda lime and baralyme producing carbon monoxide (CO) toxicity. This is more with the volatile anesthetics in the order desflurane, enflurane and then isoflurane.
- The incidence increases with **Monday's 1st case** because the absorbent becomes dry by accidentally leaving continuous gas flow through an anesthetic machine over the weekend.
- Carbon monoxide is a colorless, odorless, non-irritating gas that is easily absorbed through the lungs.
- Carbon monoxide **causes hypoxia** because hemoglobin (Hb) has 220 times greater affinity for carbon monoxide than for O₂; therefore, carbon monoxide displaces O₂ from hemoglobin forming carboxy-hemoglobin (CO-Hb) which may reach > 30%. This:
 - decreases the ability of Hb to carry O₂.
 - shifts the O₂-Hb dissociation curve to the left causing increased Hb affinity to O₂ which in turn decreases O₂ release to the tissues.

Carbon monoxide binds more tightly to fetal hemoglobin than adult hemoglobin, making infants particularly vulnerable to its effects; therefore, more care is taken in pregnant females.

Children, because of their higher metabolic rate and oxygen consumption, are also very susceptible to carbon monoxide toxicity.

Carbon monoxide also disrupts oxidative metabolism, increases nitric oxide concentrations, causes brain lipid peroxidation, generates oxygen free radicals, and produces other metabolic changes that may result in neurological and cardiac toxicity.

• Clinical picture of carbon monoxide toxicity:

1. Central nervous symptoms:

a- **Acute:** headache, nausea, vomiting, irritability, dizziness, visual/motor disturbances and decreased consciousness.

b- **Delayed:** may occur 3-21 days later in 67% of patients in the form of cognitive deficits, personality changes, and dementia, incontinence and gait disturbances.

2. Cardiovascular symptoms: tachyarrhythmias, angina especially in patients with coronary artery disease. Cherry-red lips may be present in some patients.

3. Death: occurs if CO-Hb reaches 67%.

• **Detection of carbon monoxide toxicity** is very difficult intraoperatively due to the following reasons:

1- Although the patient is hypoxic, cyanosis is not obvious because CO-Hb has a cherry red color, which is visible in the skin, mucous membranes and nail beds.

2- Pulse oximetry cannot detect the hypoxia of CO poisoning because CO-Hb and Oxy-Hb absorb light at the same wavelength (660 nm); therefore, the pulse oximeter will give a false high reading because the CO-Hb is interpreted as Oxy-Hb. Routine blood gas analysis does not recognize the presence of abnormal hemoglobins. However, CO-Hb level can be detected by **co-oximetry** (multi-wavelength oximetry) in vitro by testing a blood sample. Arterial blood sampling is not necessary since arterial and venous CO-Hb levels correlate well.

3- The clinical picture of CO toxicity is masked by the anesthesia.

4- Certain mass spectrometers and infrared anesthetic detectors (but not all) may give warnings of "mixed agent or the wrong agent", when isoflurane or desflurane degrades to carbon monoxide. Appearance of these warnings should trigger a practitioner to consider carbon monoxide formation and change the CO₂ absorbent.

• **Treatment of CO toxicity:** is limited.

1- **Oxygenation** by 100% O₂ at atmospheric pressure or by using **hyperbaric O₂**. O₂ therapy shortens the elimination half-time of carbon monoxide by competing at the binding sites for hemoglobin. It decreases the half-life of CO-Hb from 4-6 hours while breathing room air to 40-60 minutes when breathing 100% oxygen. It is administered until carboxy-Hb levels <10%.

2- Supportive treatment such as cardiovascular stabilization

Oxygen

Manufacture:

Oxygen is produced by:

1- Fractional distillation of liquid air.

2- O₂ concentrators: They produce O₂ from ambient air by absorption of N₂. The gas produced contains small quantities of inert gases (e.g., argon) which are harmless. They are used in hospitals, developing countries, military surgery, and long term domestic use in remote areas.

Physical Characters:

- It is not flammable, but supports combustion.
- It is colorless, odorless and tasteless.
- Its molecular weight is 32.

O₂ cylinders are painted black with a white shoulder. They are stored at a pressure of 137 bar at 15°C.

Physiological Effects:

See respiratory physiology.

Indications:

1- Prevention or treatment of tissue hypoxia:

Indicated: - for adults, children, and infants (older than 1 month), when PaO₂ is < 60 mmHg or SaO₂ (SpO₂) is <90% while breathing room air.

- for neonates, when PaO₂ is < 50 mmHg or SaO₂ (SpO₂) is < 88%.

Causes of tissue hypoxia are discussed later.

- 2- During anesthesia.
- 3- Indications of hyperbaric O₂: see later.

Methods of O₂ Administration:

Oxygen delivery systems are classified as variable performance or fixed performance devices.

A- Variable Performance Devices (Low Flow Devices):

These devices give variable O₂ concentration (FiO₂) according to:

- 1- The O₂ flow rate (adjusted by flowmeters).
- 2- The nasopharyngeal volume (in the nasal cannula), the mask volume (in the O₂ mask), or the volume of the oxygen reservoir bag (if present).
- 3- The patient's ventilatory pattern:

a- The amount of air/O₂ mixture delivered from the nasal cannula or the mask to the patient should exceed the **peak inspiratory flow rate (PIFR)**, otherwise more room air is inhaled and rebreathing of exhaled CO₂ occurs to meet the patient's minute ventilation needs which causes low O₂ concentration. During normal breathing, PIFR = 20-30 L/min.

PIFR increases by increasing tidal volume (deep breathing) or respiratory rate (hyperventilation).

b- If there is an **expiratory pause** between expiration and inspiration, the mask fills with O₂ and a higher concentration is available at the start of inspiration. If there is no expiratory pause, the mask acts as a dead space causing rebreathing of exhaled CO₂.

Therefore, these devices cannot perform a precise control of FiO₂ and the amount of air/O₂ mixture will be variable depending on the patient's ventilatory pattern leading to variable O₂ concentrations.

These devices are indicated for patients with:

- Minute ventilation less than ~ 8-10 L/min.
- Respiratory rates less than ~ 20 breaths/min.
- Tidal volume less than ~ 0.8 L.
- Normal inspiratory flow (10-30 L/min) i.e., low flow.

Examples:

1- Nasal Cannulas (Catheters or Prongs):

• O₂ from the cannula fills the nasopharynx or oropharynx in between breaths (both act as an O₂ reservoir with average capacity = 50 mL or about 1/3 of the anatomic dead space); therefore, during inspiration, O₂ is entrained from the nasopharynx into the trachea (thus mouth breathing does not affect FiO₂ as long as the communication between the nasopharynx and the oropharynx is patent).

• FiO₂ increases by about 1-2 %/L of O₂ delivered by the nasal cannula. It gives FiO₂ from **0.21 (at 1 L/min) up to a maximum of 0.46 (at 6 L/min)**. FiO₂ can not be increased > 0.46 whatever, the O₂ flow rate is. Therefore, O₂ flow rates > 6 L/min are not useful and when used for prolonged periods become poorly tolerated as they cause drying and crusting of the nasal mucosa (Figure 3-3).

2- Nasal Masks:

• The lower edge of the nasal mask flanges rest on the upper lip, surrounding the external nose. Nasal masks provide supplemental O₂ equivalent to the nasal cannula under low-flow conditions, but they are more comfortable to the patients (figure 3-4).

3- Non-Reservoir (Simple) Oxygen Masks:

• A minimum of 5-6 L/min O₂ flow rate is necessary to prevent rebreathing of exhaled CO₂ and clear exhaled gas from the mask. Its reservoir capacity is usually 150-250 mL. It fits loosely on the face, which allows room air to be inhaled, if needed.

It can deliver FiO₂ 0.3 (at 5 L/min) up to FiO₂ 0.5-0.6 (at 6-10 L/min) (figure 3-5).



Figure 3-3: Nasal catheter



Figure 3-4: Nasal mask

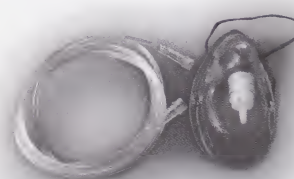


Figure 3-5: Simple O₂ mask

Reservoir Masks:

These devices are tight seal masks with large reservoir bags (with a capacity of 750-1250 mL) and valves. If the reservoir bag is kept inflated, the patient will inhale only the gas contained in the bag.

a. Partially rebreathing masks:

- It is a face mask connected to a large volume reservoir bag.
- It contains a unidirectional expiratory valve on the side of the mask to prevent entrainment of room air during inspiration and allow exhaled gas to go outside the mask (figure 3-6). This device allows the gas exhaled in the initial phase of expiration to return to the reservoir bag. As exhalation proceeds, the expiratory flow rate declines and falls below the oxygen flow rate where exhaled gas can no longer return to the reservoir bag. The initial part of expiration contains gas from the upper airways (anatomic dead space), so the gas that is rebreathed is rich in oxygen and markedly devoid of CO₂.
- This system can deliver **FiO₂ 0.35 (at 5-7 L/min) up to FiO₂ 0.8 (at 15 L/min)**.

b. Totally non-rebreathing masks:

- As above but, it contains 2 unidirectional valves (figure 3-7):
 - expiratory: as above and
 - inspiratory: between the mask and the reservoir bag, to prevent entry of any exhaled gas into the reservoir bag and allow inspiration.
- O₂ flow should be enough to prevent complete collapse of the bag during inspiration.
- This system can deliver **FiO₂ 0.4 (at 5-7 L/min) up to FiO₂ 1.0 (at 10-15 L/min)**.



Figure 3-6: Partially non-rebreathing mask



Figure 3-7: Totally non-rebreathing mask

Fixed-Performance Devices (High-Flow Devices):

These devices give a preset (fixed) O₂ concentration (FiO₂) at high flow rates by providing a sufficiently large reservoir of premixed gas. The delivered FiO₂ is not affected by changes in the patient's ventilatory pattern.

Although O₂ is delivered to the mask at low flow rates, the O₂ is passed at the inlet of the mask through a narrowed orifice and this creates a high-velocity stream of gas.

Presence of holes in the mask entrains air with O₂ by **the Bernoulli Effect** as O₂ stream creates sub-atmospheric pressure which increases the total air/O₂ flow rate to exceed PIFR. FiO₂ becomes non-dependent on the patient's ventilatory pattern.

Therefore, fixed O₂ concentration is produced which depends now only on O₂ flow rate and size of holes. These devices are indicated in patients who need:

- Consistent FiO₂ such as patients with chronic hypercapnia because an inadvertent increase in FiO₂ in these patients can lead to further CO₂ retention.
- High inspiratory flow rates of gas (> 40 L/min).

- Examples:

1- Air-Entrainment Venturi Masks:

- Principles: see above.
- If there is a low O₂ flow rate with wide side ports, more amount of air will be entrained which decreases FiO₂ and the reverse is true; if there is a high O₂ flow rate with narrow side ports, less amount of air will be entrained which increases FiO₂ (figure 3-8).



Figure 3-8: Venturi mask

40

- FiO_2 can be increased by about 2% (above atmospheric $\text{O}_2 \sim 20\%$) for every one L/min O_2 flow rate.
- | | | |
|------------|-----|---|
| To achieve | 24% | O_2 flow rate is adjusted at 2 L/min |
| | 28% | O_2 flow rate is adjusted at 4 L/min |
| | 35% | O_2 flow rate is adjusted at 8 L/min |
| | 40% | O_2 flow rate is adjusted at 10 L/min |
| | 60% | O_2 flow rate is adjusted at 15 L/min which is enough. |

- Value: to give constant FiO_2 e.g., during weaning, especially in patients with chronic obstructive pulmonary diseases (COPD).

2- Air-Entrainment Nebulizers:

- They produce aerosol with fixed FiO_2 .
- They use a jet and an adjustable orifice to vary entrained air to get various levels of FiO_2 .
- They can provide FiO_2 as Venturi masks.

3- High-Flow Air/ O_2 Systems "Continuous Positive Airway Pressure (CPAP) Masks":

They are either face or nasal CPAP masks. They are discussed in more details in the chapter of "Intensive (Critical) Care".

4- Anesthesia Bag or Bag-Mask-Valve System:

- Anesthesia bags are 1-, 2-, 3-L non-self-inflating reservoirs with a tail piece gas inlet.
- Self-inflating resuscitation bags use a unidirectional gas flow.
- These devices can deliver FiO_2 1.0.

N.B.: Others Methods of O_2 Administration:

1- **Head tent or O_2 hood:** it covers only the head and can deliver 50-80% especially in pediatrics.

2- **T-piece:** it is connected to a tracheostomy or an endotracheal tube.

3- **Bi-level positive airway pressure (B.I.P.A.P.) nasal or face mask:** it has a valve which sets 2 pressure levels.

4- **Method of administration of hyperbaric O_2 :** see down.

N.B.: To estimate the normal PaO_2 at different values of FiO_2 , we may assume that every 10% of O_2 concentration increases PaO_2 about 50-60 mm Hg.

For example: when FiO_2 is 1.0, normal PaO_2 should be 500-600 mmHg.

and when FiO_2 is 0.4, normal PaO_2 should be 200-240 mmHg.

Hazards (Adverse Effects) of O_2 Therapy:

1. Fires:

O_2 supports combustion of fuels causing conflagrations or explosions.

2. Respiratory Effects:

1. Absorption Atelectasis:

- High FiO_2 can cause pulmonary atelectasis in areas distal to the site of airway closure.
- As O_2 is highly soluble in blood it replaces N_2 in the low ventilation/perfusion areas causing decreased alveolar volume.
- High FiO_2 on induction of anesthesia i.e., preoxygenation significantly contributes to the formation of absorption atelectasis; therefore, it is recommended to:
 - reduce the FiO_2 to less than 80%,
 - apply CPAP during preoxygenation,
 - place the patient in anti-Trendelenburg position.

2. Hypoventilation:

In patients with COPD and chronic CO_2 retention depending on hypoxic drive from the peripheral chemoreceptors (that respond to O_2), there is loss of sensitivity of central chemoreceptors. So, High FiO_2 causes loss of peripheral chemoreceptor drive which in turn causes ventilatory failure and CO_2 narcosis.

3. Oxygen Toxicity:

It is discussed later.

Hyperbaric Oxygen Therapy

It is administration of O_2 at a pressure of 2-3 atmospheres (atmospheric pressure = 760 mmHg).

Effects:

At one atmospheric pressure, PaO_2 is 100 mmHg, where the amount of O_2 physically dissolved in plasma = 0.3 mL/dL.

At 2.5-3 atmospheric pressure, PaO_2 is > 400 mmHg, where the amount of O_2 physically dissolved in plasma = 5.5 mL/dL.

Therefore, O_2 consumption (5mL/dl) can be theoretically met by the plasma only.

Indications:

- 1- Carbon monoxide or cyanide poisoning.
- 2- Anerobic infection e.g., gas gangrene, tetanus or chronic osteomyelitis.
- 3- Anemia as severe anemia, sulph-or met-hemoglobinemia.
- 4- Malignancy where O_2 increases sensitivity of malignant cells to irradiation.
- 5- Decompression sickness and air embolism.
- 6- Congenital heart disease to correct hypoxia.
- 7- Ischemia as ischemic skin grafts, peripheral arterial ischemia, or hypoxic wounds.

Methods of Administration:

Pressurized chambers exposing the patient to O_2 tension > atmospheric pressure are used. It is either:

- 1- One-person hyperbaric chamber: 100 % O_2 is used to pressurize the chamber
- 2- Multi-place hyperbaric chamber: Air is used to pressurize the chamber while the patient is breathing 100% O_2 via a mask or an endotracheal tube. This allows the medical personnel to stay with the patient (figure 3-9).

Anesthetic Considerations in the Hyperbaric Atmosphere:

Technique:

General anesthesia is preferred because regional anesthesia increases the risk of sepsis and there is a difficulty in communication with the patient, but there is no effect on the pharmacokinetics of local anesthetics or intravenous anesthetic agents.

Induction:

Intravenous induction is preferred because inhalational induction may produce:

- chamber pollution.
- fire and explosion with flammable agents (it is not used now).

The cuff of endotracheal tubes should be filled with fluid or saline to avoid volume changes when the pressure is elevated. If it is filled with air, reduction of the gas volume of the cuff may increase the risk of aspiration.



Figure 3-9: A one-person hyperbaric chamber (left image) and a multi-place hyperbaric chamber (right image)

Maintenance:

Opioid based anesthesia or non-flammable **inhalational** anesthesia is preferred.

N₂O should be avoided because it increases the risk of emboli (as N₂O is 35 times more soluble in blood than O₂) especially on decompression of the chamber.

Intravenous Fluids:

Plastic bottles are preferred, as glass bottles may fracture by the compression unless the bottle is vented by a needle.

Careful observation of the meniscus of the drip chamber is needed because it moves upwards during compression and downwards during decompression into the i.v. tubing. This may cause air embolism.

Equipment:

- Vaporizers: They deliver the same concentration.
- Ventilators: Pneumatically driven are preferred because electrically driven may cause sparks and fire.
- Diathermies: are used cautiously to avoid sparks and fire.
- Defibrillators: are used cautiously to avoid sparks and fire.

Low resistance gel should be applied to the paddle because high resistance gel, if used, causes greater heat production at the paddle/skin interface.

- Rotameter: hyperbaric condition elevates the density of the gases which increases the power that lifts the bobbin; therefore, false readings occur (i.e., the delivered flow is < the indicated flow). It is recommended to recalibrate the Rotameter.

N.B.: No need to readjust the vaporizer as it gives the same %.

Monitoring:**1- Arterial blood pressure:**

- An aneroid gauge is preferred to a mercury column to avoid the risk of mercury spillage in the chamber.
- Chamber compression causes increased ambient pressure which alters the zero effect of the pressure transducer. Therefore, the pressure transducer should be re-zeroed immediately after compression.

2. Pulmonary artery catheter:

- The balloon port should be always kept open.
- The balloon cuff should never be filled with fluid (already filled with 1.5 mL air) because this may cause rupture of the pulmonary artery.

3. Arterial blood gases:

- It is recommended to measure the arterial blood gases inside the chamber or a correction factor is needed because the gases differ in their solubility according to the atmospheric pressure.

Oxygen Toxicity (Hyperoxia) (Oxygen Free Radicals)

It is also called "**Paul Bert effect and Lorrain Smith effect**" after the researchers who pioneered its discovery and description in 1878. The condition was first discovered in scuba divers who consumed high oxygen concentrations.

Definitions**A Free Radical:**

- It is an atom or molecule (e.g., oxygen, nitrogen) **with one or more unpaired electron in the outermost shell (orbital)** and is capable of independent existence, hence, the name free.
 - Free radicals tend to be **highly reactive species** because of their unpaired electrons, which allow them to steal electrons from the surrounding tissues and molecules i.e., they have a high oxidant activity.
- The radical molecule is reduced by gaining the electron while the other molecule is oxidized by losing the electron.

Reactive Oxygen Species:

- They are free radicals that are **derived from oxygen metabolism** inside the mitochondria and contain an **oxygen center in their structure**.

An Oxygen Molecule

It consists of: 2 atoms ($O + O = O_2$). Each atom contains 8 electrons distributed as follows:

- The three inner orbitals contain paired electrons spinning in opposite directions (6 electrons).
- The two outermost orbitals contain unpaired electrons spinning in the same direction (2 electrons) (figure 3-10).

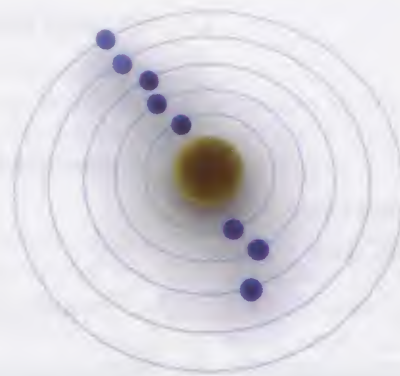


Figure 3-10: An oxygen atom

- Oxygen is a free radical, but it is not highly reactive (i.e., a weak oxidizing agent) because the two unpaired electrons spin in the same direction. This decreases the ability of oxygen molecule to accept a new electron.

- According to Wolfgang Pauli's Exclusion Principle, no two electrons can occupy the same orbital if they have the same directional spin; and for an atom or molecule, to accept electrons, the outer orbital should have 2 electrons of opposite spin.

This means that it is impossible to add an electron pair to oxygen and reduce it to water in a one-step reaction because one orbital would have two electrons with the same directional spin.

This spin restriction limits O_2 molecule to make single electron additions, which:

- increase the number of reactions needed to reduce molecular oxygen to H_2O .
- and - produce more highly reactive intermediates.

N.B.: Electrons tend to spin in pairs.

Oxygen Metabolism:

- An atom is considered to be "ground" when every electron in the outermost shell has a complimentary electron that spins in the opposite direction.

- Free radicals tend to steal an electron from a surrounding compound or molecule; therefore, a new free radical is formed in its place. In turn, the newly formed radical steals another electron trying to reach the ground state. This occurs through thousands of reactions which are called the **electron transport chain (ETC)**. These reactions occur **in the mitochondria** and utilize oxygen to generate energy in the form of adenosine triphosphate (ATP) with production of unwanted electrons that accumulate.

- The oxygen molecule gets rid of these unwanted electrons and is reduced to water. Complete reduction of oxygen molecule to H_2O requires addition of 4 electrons in the outer orbitals + 4 protons (figure 3-11).

- Normally, about 98% of the oxygen in mitochondria is reduced completely to water, and less than 2% of the **total oxygen intake** has the ability to form the **highly damaging reactive oxygen metabolites** (which escape into the cytoplasm) as natural byproducts of the normal metabolism of oxygen.

1. Ground-State Oxygen (O_2):

It is a free radical (having 2 unpaired electrons), but not highly reactive (weak oxidizing agent) because the 2 unpaired electrons spin in the same direction.

2. Super-Oxide Anion (Radical) ($O_2^{\bullet -}$):

It is a less free radical than O_2 (as it has one unpaired electron).

It is neither highly reactive nor a potent oxidant. It is implicated in reperfusion injury after ischemia.

3. Hydrogen Peroxide H_2O_2 ($O_2^{\bullet -2}$):

It is not a free radical (as it does not have any unpaired electrons), so it is not reactive.

It is highly mobile and crosses the cell membrane easily where it may change to one of the following:

- Hydroxyl radical ($\bullet OH$) which is highly oxidant.
- Singlet oxygen (1O_2).
- Water by the glutathione peroxidase or catalase enzymes.

Iron in the reaction is considered as a powerful pro-oxidant.

4. Hydroxyl Radical ($\bullet OH$):

It is the ace of free radicals. It is the most reactive molecule known to biochemistry and can oxidize any molecule in the body. It is not mobile.

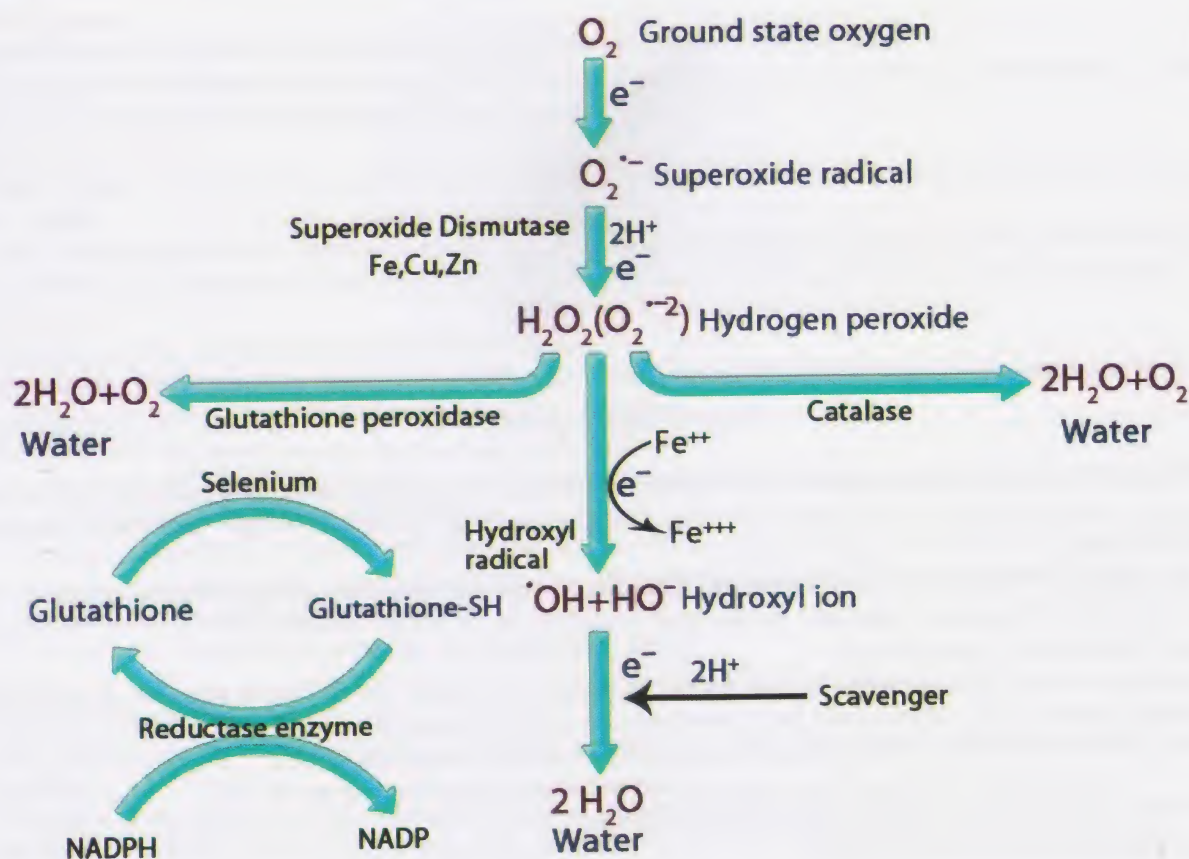


Figure 3-11: O_2 metabolism and the antioxidant defense mechanisms

Types of O_2 Free Radicals:

- 1- Super-oxide radical ($O_2^{\bullet -}$).
 - 2- Hydrogen peroxide (H_2O_2) ($O_2^{\bullet -2}$): It is not a free radical, but it gives powerful cytotoxic compounds.
 - 3- Hydroxyl radical ($\bullet OH$).
 - 4- Singlet oxygen (1O_2): it is an excited form of oxygen in which one of the electrons jumps to a superior orbital following absorption of energy.
 - 5 - Hydro-chlorous acid ($HOCl$) in neutrophils.
 - 6- Nitric oxide (NO).
 - 7- Carbon monoxide (CO).
- N.B.: N_2O = Nitrous oxide. NO = Nitric oxide. NO_2 = Nitrogen dioxide. N_2 = Nitrogen.

Sources of O_2 Free Radicals:

a- Endogenous Sources:

- 1- Arachidonic acid oxidation (the most important source)

Arachidonic acid $\xrightarrow{\text{Cyclo-oxygenase oxidation}}$ prostaglandins, thromboxane A_2 , and O_2 free radicals

- 2- Cellular respiration (mitochondria)

98% of O_2 molecules $\xrightarrow{\text{Cytochrome oxidase (complete reduction)}}$ H_2O

2% of O_2 molecules $\xrightarrow{\text{Single electron reduction (incomplete reduction)}}$ O_2 free radicals

Large amounts of free radicals are produced when the cells are exposed to abnormal conditions such as hypoxia or hyperoxia.

- 3- Neutrophil activation: neutrophils specialize in producing oxygen free radicals, which are used in host defense to kill invading pathogens.

- 4- Oxidant enzymes: xanthine oxidase and monoamino oxidase, which produce large amounts of free radicals.

b- Exogenous Sources:

- 1- Drugs: e.g., bleomycin.
 - 2- Toxins and pollutants: e.g., cigarette smoking (tar).
 - 3- Ionizing radiation: it generates large amounts of oxygen free radicals. It is observed that the damaging effects of radiation are higher in well oxygenated tissues than in tissues deficient in oxygen.
- In the previous conditions, there is over production of free radicals in cells.

Function of Free Radicals

Although they appear harmful to the body, they are produced to do important functions as follows:

- They help neutrophils in phagocytosis to kill invading pathogens. During activation of the inflammatory response (such as during the acute respiratory distress syndrome "ARDS" and the systemic inflammatory response syndrome "SIRS"), granulocytes are activated. This activation is associated with an increase in O_2 consumption (up to 20-fold) which is known as the "**respiratory burst**". The increase in O_2 consumption is associated with more production of **toxic oxygen metabolites**, which are stored in cytoplasmic granules. These metabolites are released as part of the inflammatory response and can **damage invading microorganisms** i.e. these toxic oxygen metabolites have been implicated in the **inflammatory-mediated cell injury**.
- They are involved in intercellular and intracellular signaling. For examples: addition of superoxide or hydrogen peroxide to a variety of cultured cells leads to an increased rate of DNA replication and cell proliferation i.e., these radicals function as mitogens.

Defense Mechanisms (Anti-Oxidants):

- Under normal conditions (at rest), the antioxidant defense mechanisms that are naturally occurring within the body can easily handle free radicals that are produced, and cells are normally able to defend themselves against the oxygen free radicals.
- During times of increased oxygen flux (i.e., exercise or increased oxygen intake), free radical production can increase dramatically and may exceed the ability of the defense mechanisms, ultimately resulting in **oxidant stress** and producing tissue and cell damage.
- **Antioxidants:** are effective because they are willing to give up their own electrons to free radicals; therefore, the free radicals will produce no more effects on other tissues e.g., a cell membrane (figure 3-12).

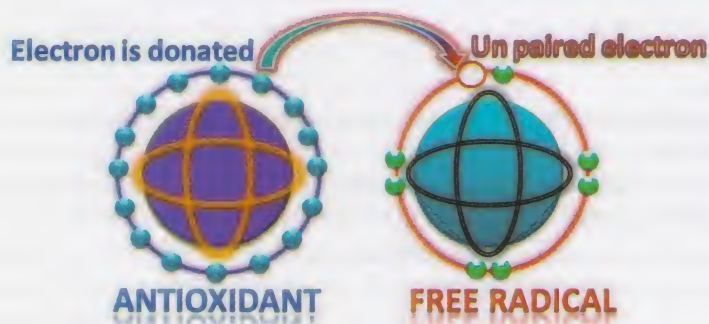


Figure 3-12: The action of antioxidants

There are two main categories of antioxidants:

A- Enzymatic Anti-Oxidants:**1- Superoxide dismutase:**

- It catalyzes the conversion of superoxide anion to hydrogen peroxide which is less toxic than superoxide anion.
- It needs cofactors which are iron (Fe), copper (Cu), zinc (Zn), and manganese (Mn).

2- Catalase:

- It reduces H_2O_2 into H_2O .
- It is present in most cells, but lowest in cardiac cells and neurons.

3- Glutathione peroxidase:

- It reduces H_2O_2 into H_2O by removing an electron from glutathione in its reduced form (GSH) and donating it to H_2O_2 .

The oxidized glutathione is then returned back to its reduced state by a reductase enzyme that transfers the reducing equivalents from NADPH.

- **Selenium (Se):** is a cofactor for the glutathione peroxidase enzyme. Its normal range in blood is 0.5-2.5 mg/L. It is an essential trace element with recommended dietary allowance of: 70 µg/day for males.
50 µg/day for females.

B- Non-Enzymatic Anti-Oxidants:

a- Fat Soluble Antioxidants:

1- Vitamin E:

It is a lipid soluble vitamin and **the most potent antioxidant**. Its normal plasma level is 1 mg/dL (< 0.5 mg/dL = deficiency).

Action: It is the major antioxidant protection against oxidant damage to the lipid cell membrane by blocking propagation of lipid peroxidation in cell membranes (see later).

Mechanism: - When a propagating wave of lipid peroxidation in cell membrane phospholipids reaches vitamin E, the latter is oxidized into a free radical sparing adjacent polyunsaturated fatty acids from oxidation. Vitamin E radical is poorly reactive; therefore, it is a chain-breaking antioxidant.

- Vitamin E radical is reduced by vitamin C (acting as an electron donor) into vitamin E.

2- Vitamin A.

3- β-carotene.

b- Water Soluble Antioxidants:

1- Glutathione:

It is a sulfur containing tri-peptide (glycine-glutamine-cysteine). It is a reducing agent by means of a -SH group on a cysteine residue. It is a major intracellular anti-oxidant (present in a molar concentration of 0.5-10 nmol/L in most cells). It is synthesized de novo in cells and does not easily cross the cell membrane; therefore, exogenous glutathione has little effect on the intracellular level. Therefore, it is of limited therapeutic value.

2- Vitamin C (Ascorbic acid):

It is abundant in the lung.

Action: - It acts as a reducing agent. It donates electrons to the free radicals filling their orbitals.

- It operates primarily in the extracellular compartment.

- It participates in recycling vitamin E radicals.

- It also acts as a pro-oxidant in the presence of iron i.e., it facilitates formation of oxidants.

Mechanism: Vitamin C reduces iron into Fe^{++} to facilitate its absorption from the intestine. Fe^{++} promotes the production of hydroxyl radical from H_2O_2 by donating an electron to H_2O .

c- Other Antioxidants:

1- Plasma antioxidants:

a- **Ceruloplasmin** (Cu transport or storage protein): It oxidizes iron from the Fe^{++} to Fe^{+++} state.

b- **Transferrin:** It binds iron in Fe^{+++} state.

Both "a" and "b" decrease free iron in plasma as free iron can promote oxidant cell injury by enhancing the formation of hydroxyl radicals.

c- **Albumin:** It is a potent scavenger of hydro-chlorous acid (HOCl).

2- Bilirubin.

3- Uric acid.

4- Carotenoids.

Pathological Effects of Oxygen Toxicity (Free Radical Reactions):

These effects depend on the FiO_2 and the duration of exposure especially if hyperbaric oxygen is administered as this extremely elevates the PaO_2 to toxic levels and produces a state of **oxidant stress**.

A- Cellular Injury:

1- Lipid peroxidation reactions: a free radical prefers to steal electrons from the phospholipid membrane of a cell especially polyunsaturated fatty acids (PUFA) causing lipid peroxidation reaction. The process starts at one site and then **propagates** to the entire cell membrane. This reaction causes:

- increased cell membrane rigidity (as PUFA are responsible for cell membrane fluidity).
- decreased activity of membrane-bound enzymes (e.g., sodium pump).
- altered activity of membrane receptors.
- altered membrane permeability to ions.

Finally, the cell membrane loses its integrity and the cell is destroyed.

2- Apoptosis (Programmed cell death).

3- DNA affection: by causing chromosomal deletion, mutations, and cell death.

4- Denaturation of intracellular proteins.

Tissue Damage:**1- Central Nervous System Oxygen Toxicity:****1- High pressure nervous syndrome:**

- Visual changes (especially tunnel vision).
- Ringing in the ears (tinnitus) and vertigo.
- Nausea.
- Personality and mood changes, and anxiety.
- Muscle twitches, (especially in the face), irritability, dizziness, confusion, and **convulsions**. This is followed by a period of loss of consciousness.

This may occur within 30 minutes at 3 atmospheric pressure. Therefore, give 2-2.5 atmospheric pressure for 1-2 hours interrupted with periods of rest.

It is treated by: - withdrawal of O₂ and breathing air.

- gradual decompression.

2- Cerebral strokes and ischemia.**2- Pulmonary Oxygen Toxicity:**

- Hyperemia of the nasal mucosa.
- Irritation of the nose, pharynx, and trachea.
- Tracheobronchitis.
- Inhibition of mucociliary mechanisms which causes retention of secretions.
- Acute respiratory distress syndrome- like "ARDS-like" injury of the alveolar capillary membrane: The injury is dependent on:
 - Partial pressure of O₂ (alveolar is more important than arterial PO₂).
 - Duration of exposure: Although FiO₂ of 1 for up to 10-20 hours is considered safe at one atmosphere, FiO₂ > 0.5 for periods 16-24 hours at a higher pressure can cause toxicity.

- Bronchopulmonary dysplasia in infants.

In addition to other respiratory effects (not toxicity):

- Absorption atelectasis.
- Hypoventilation that occurs in patients with COPD.
- Increased airway resistance and work of breathing due to increased gas density by the hyperbaric condition.

3- Cardiovascular Oxygen Toxicity:

- **Vasoconstriction** of peripheral, cerebral, coronary, renal and hepatic vessels (except pulmonary vessels where vasodilation occurs); if PaO₂ increases > 225 mmHg (30 kPa).

N.B.: Hypoxia, hypercapnia, acidosis, and histamine release cause **vasodilatation** of all blood vessels of the body **except the pulmonary blood vessels** where vasoconstriction occurs, and the reverse is true.

- **Myocardial depression** may occur which results in acute heart failure and pulmonary edema, especially in patients with severe cardiovascular disease, if PaO₂ is increased > 600 mmHg.

4- Retrolental Fibroplasia: (in neonates especially premature)

- It correlates with the partial pressure of arterial O₂ (PaO₂) better than the partial pressure of alveolar O₂ (PAO₂) (unlike pulmonary toxicity).
- PaO₂ < 140 mmHg is considered safe.
- Mechanism and pathology:

Increased PaO₂ causes vasoconstriction of the retinal vessels which in turn obliterates the most immature retinal vessels. This is followed by subsequent new vessel formation at the site of damage with proliferative retinopathy which causes leakage of intravascular fluid leading to vitreo-retinal adhesions and fibrosis. Later on, retinal detachment occurs.

5- Hemopoiesis Depression:

- High FiO₂ for long time causes depression of hemopoiesis leading to anemia.

6- Endocrine Effects:

- There is a decrease in the thyroid stimulating hormone (TSH) and thyroid hormone (T₄) and an increase in the cortisol levels.

7- Metabolic Effects:

- The enzymatic activities are reduced causing altered GABA metabolism and impaired metabolism of SH-group which is necessary for glycolysis.

8- Other Effects:

- Carcinogenesis.

- Aging and atherosclerosis.
- Reperfusion injury of transplanted organs.
- Renal impairment.
- Liver impairment

In addition to **decompression sickness** that occurs to patients and other personnel in the hyperbaric chamber (it is not toxicity).

Management:

A- Prevention:

1- FiO₂:

- Avoid administration of FiO₂ > 0.6 as it is accompanied with high risk of O₂ toxicity.
- So, if O₂ is used > 60%, it should not be used for > 2-3 days (e.g., in intensive care).

If O₂ is used < 60%, O₂ toxicity still can occur especially when the defense mechanisms are impaired as in critically ill patients.

N.B.: The optimal FiO₂ is the lowest FiO₂ (< 0.6) which the patient can tolerate.

2. Antioxidant Status:

- Serum levels of vitamins A, C, E, and selenium should be assessed and any deficiency should be replaced.
- Antioxidants can be supplied from food such as fruits, vegetables, seeds, nuts, meats, and oil.

B- Curative: By antioxidant drugs (free radical scavengers).

1- Vitamins A, C, E and Selenium.

They are the only available natural antioxidants.

Supplemental selenium can be given as Na selenite i.v. with a maximal dose of 50 µg/6 h.

2- Glucocorticoids (Methyl prednisolone)

It is effective in acute spinal cord injury, if given within 8 hours.

Mechanism: - It inhibits lipid peroxidation.

Dose: High: 30 mg/kg i.v. (mega dose).

3- Aminosteroids: Lazaroids e.g., Tirilizad

Advantage: • It is 100 times more potent than methyl prednisolone.

- It does not have no side effects of methyl prednisolone.

Mechanism: It inhibits lipid peroxidation, so acts as an antioxidant.

Dose: The initial dose is 1 mg/kg and the maintenance dose is 0.5 mg/kg.

4- N-acetyl cysteine:

It is a **popular mucolytic agent**. It is used as an antioxidant because it is a **glutathione analogue** capable of **crossing cell membranes** and enhancing intracellular glutathione activity. Therefore, it is **used in acetaminophen toxicity**.

5- Others: • Desferrioxamine: It chelates Fe⁺⁺ causing inhibition of OH formation.

- Xanthine oxidase inhibitors e.g., allopurinol.
- Dimethyl sulfoxide: It causes OH scavenging.
- β- carotenoids.
- Probucol.
- Oxypyridin.

Carbon Dioxide (CO₂)

Manufacture:

- 1- As a byproduct of fermentation in brewing of beer.
- 2- As a byproduct of manufacture of hydrogen.
- 3- By heating Mg and Ca carbonate in presence of their oxides.
- 4- As a combustion gas from burning fuel.

CO₂ Cylinders:

- Grey cylinders containing liquid CO₂ at 50 bar pressure.
- The filling ratio is 0.75 and the liquid phase occupies about 90-95% of the cylinder capacity.

Physical Characters:

- Colorless and with pungent odor.
- M.W. 44, critical temperature 31°C, and critical pressure 73.8 bar.

Physiological Effects:**1 - Respiratory Effects:** (see respiratory physiology)

- CO₂ increases rate and depth of respiration. It acts directly and reflexly via chemo-receptors. This effect is maximal at 5-7%.
- CO₂ has an expectorant action as it liquefies sputum.

2- Cardiovascular Effects:

It produces changes similar to those induced by pain or light anesthesia.

As regards cardiac output, arterial blood pressure, and heart rate, there is a **biphasic response** (they increase, then after > 75 mm Hg CO₂ they decrease):

- Increased PaCO₂ (up to 75mmHg) causes a progressive increase in cardiac output, blood pressure and heart rate due to indirect sympathetic stimulation.
- PaCO₂ > 75 mmHg causes a decrease in these parameters due to direct myocardial depression.

b- Vasodilatation of cutaneous, cerebral, coronary, and gastrointestinal vessels (not pulmonary vessels) occur due to elevation of CO₂ levels.

3- Central Nervous Effects:

- At low levels, CO₂ depresses the excitability of the cerebral cortex.
- At high levels, it activates sub-cortical centers causing convulsions.
- At higher levels, it causes depression of the central nervous system.

4- Gastrointestinal Effects:

- CO₂ produces an irritant effect on gastrointestinal mucosa resulting in an increase in its secretions (and HCl).

Therapeutic Uses:

It is used by special CO₂ flowmeters (5-7% CO₂ in O₂) (*Carbogen*).

- 1- In carbon monoxide poisoning: as it increases respiratory exchange and increases the rate of carbon monoxide dissociation from carboxy-Hb.
- 2- As an expectorant, in treatment of hiccup, petit mal epilepsy and locally to destroy warts (solid form at -80°C as dry ice).
- 3- In anesthesia.

Nowadays, the use of CO₂ is decreased in anesthesia due to its risks;

- It increases the speed of induction and recovery from inhalational anesthesia as it increases the respiratory minute volume.
- It facilitates blind nasal intubation as it increases ventilation.
- It assists reinstitution of spontaneous ventilation after a period of artificial hyperventilation.
- During carotid artery surgery, it increases cerebral blood flow. There is a controversy, as increased PaCO₂ may cause stealing of blood away from an ischemic area of brain; therefore, anesthesiologists may prefer to maintain normocapnia during this surgical procedure.

Contraindications:

- 1- Respiratory: COPD patients as they are already hypercapnic.
- 2- Cardiovascular: pulmonary edema and hemoptysis due to vasodilatation.
- 3- Neurological: cerebral injuries and space-occupying lesions of brain due to vasodilatation.
- 4- Gastrointestinal: peptic ulcer (also carbogenated beverages are avoided).

Toxicity of CO₂ (Retention of CO₂):

It is most common in patients with chronic emphysema who no longer respond to the normal respiratory effect of alveolar CO₂.

Clinical picture: CO₂ accumulation occurs that results in respiratory acidosis.

Treatment:

- 1- Mechanical ventilation.

2- Toluol: Tri-hydroxyl-methyl amino methane (THAM)

- It is an amine buffer that acts as a proton acceptor.
- It unites with carbonic acid resulting in formation of bicarbonate.
- Dose: 300 mL i.v. infusion over 1 hour as 0.3 M solution.

Helium

Physical Characters:

- It is an inert gas.
- It has low density = 0.16 (density of O₂ = 1.3)

Effects:

- Mixtures of helium (80%) and O₂ (20%) can be inhaled to decrease the work of breathing and enable O₂ to pass via the obstructed passages with the least effort e.g., upper respiratory tract obstruction or status asthmaticus.

- Because during obstruction, the flow becomes turbulent, using a gas mixture with low density decreases turbulence and may change flow to laminar. This produces easier diffusion of the gas mixture.

N.B.: Turbulent flow (Reynolds' number) \propto density.

INTRAVENOUS ANESTHETIC AGENTS

Pharmacokinetics of Intravenous Anesthetics

Absorption:

Intravenous route completely bypasses the process of absorption as drugs are placed directly into the blood; therefore, it produces very high bioavailability, but with other routes such as oral, subcutaneous, or intramuscular, the bioavailability differs according to the route (bioavailability is the fraction of unchanged drug that reaches the systemic circulation).

Distribution:

• After intravenous (i.v.) injection, a drug is distributed to different tissues according to their blood supply; see before the types of tissues according to their blood supply.

• At first, the drug is distributed to the brain and other organs as heart, kidney, brain, and liver (vessel-rich tissues); where the drug diffuses from the arterial blood across the blood-brain barrier into the brain. The rate of the drug across the blood-brain barrier depends on:

a- **Blood flow to the brain:** reduced cerebral blood flow (CBF) e.g., carotid artery stenosis or low cardiac output, results in reduced delivery of the drug to the brain.

b- **Diffusion across the blood-brain barrier:** This in turn, depends on:

1- **Protein binding:** only an unbound drug is free to cross the blood-brain barrier.

2- **Degree of ionization:** only the non-ionized fraction of the drug can cross the lipid blood-brain barrier. The degree of ionization of the drug depends on the pH of extracellular fluid and the pKa of the drug.

The pKa of the drug is the pH of the medium, at which the dissociated (ionized) and un-dissociated (unionized) fraction forms of the drug are present at equilibrium e.g., if the pKa of the drug is 8 and it is injected in the plasma where the pH is 7.4, the ionized fraction will be deviated from the 50% either more or less i.e., the ionized fraction may be 60% according to the drug. If the pKa of the drug is 7.4 and it is injected in the plasma where pH is 7.4, also the ionized fraction will be 50%.

3- **Lipid solubility:** high lipid soluble drugs pass the blood-brain barrier easier than the less lipid soluble drugs.

4- **Molecular weight of the drug:** drugs with smaller molecular weight pass the blood-brain barrier easier than drugs with higher molecular weight.

• After the initial distribution of the drugs to the brain and other vessel-rich tissues (which are now saturated with the drug), distribution occurs into **muscles (lean)**, which is slower due to their low lipid content, but is quantitatively important due to their relatively good blood supply and large mass.

• Then the drug is distributed into **fat** which is also slow due to its poor blood supply, despite its high lipid content. Fat contributes little to the initial redistribution or termination of action of i.v. anesthetic agents, but fat depots contain a large proportion of the injected dose.

• After that, the plasma concentration of the drug falls; therefore, some drug leaves the highly perfused organs to maintain equilibrium according to the concentration gradient. This **redistribution** from the vessel-rich group is responsible for termination of the effect of many i.v. anesthetic agents e.g. awakening from effects of thiopentone is not due to metabolism or excretion but rather to redistribution of drug from brain to muscle.

• On repeated doses of drug, saturation of less perfused organs occurs; therefore, redistribution can not occur and awakening will depend to a greater extent upon drug elimination and metabolism, so rapid-acting drugs such as thiopentone and fentanyl will become longer acting after repeated administration or when a large single dose is given.

Biotransformation (Metabolism):

• The liver is the primary organ of metabolism.

• If metabolism is rapid (indicated by a short elimination half life), it may contribute to some extent to the recovery of consciousness.

• Due to the large distribution volume of i.v. anesthetic drugs, total elimination takes many hours or days.

Excretion:

• It occurs mainly to end water-soluble metabolites through the kidneys.

• Only a small % of drugs are excreted unchanged in the urine.

Compartmental Models

Definition:

- It is a simple way to determine the distribution and elimination of drugs in the body.
- A compartment is a virtual space as it represents a group of tissues that possess similar Pharmacokinetic characteristics e.g.,
 - the vessel-rich group as a central compartment, and
 - the vessel-poor group as muscle, fat, and skin as a peripheral compartment.

Therefore, compartments are conceptual and do not represent actual tissues.

- Drugs may follow a two-, a three-, or more compartmental models. Most intravenous anesthetic drugs follow three-compartmental models.

A) A Two-Compartmental Model: It consists of two phases (figure 3-13):

1- The Distribution Phase or Alpha " α " Phase:

After an intravenous bolus, there is a sharp rise of plasma concentration which declines rapidly due to the redistribution of drug from the plasma and the vessel-rich group of the central compartment to the less perfused tissues of the peripheral compartment. The duration of this phase represents the distribution half-time or alpha half-life ($t_{1/2\alpha}$).

2- The Elimination Phase or Beta " β " Phase:

After the distribution phase, the plasma concentration declines in a less steep manner due to elimination of the drug. The duration of this phase represents the elimination half-life ($t_{1/2\beta}$).

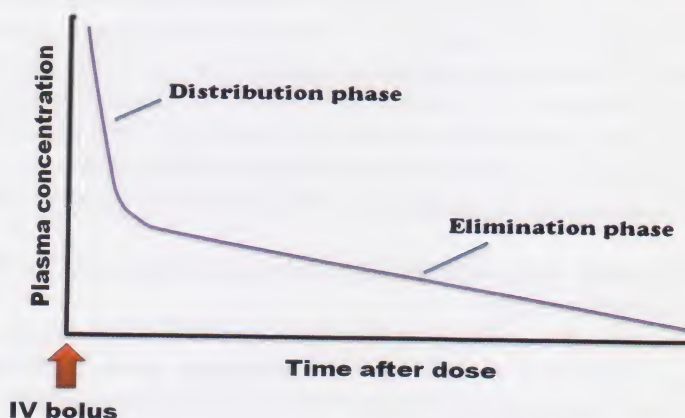


Figure 3-13: A two compartmental model

B) A Three-Compartmental Model:

It best describes the intravenous anesthetic drugs as propofol. It consists of three phases:

- 1- **An alpha phase:** corresponds to the rapid distribution half-life ($t_{1/2\alpha}$).
- 2- **A beta phase:** corresponds to the slow distribution half-life ($t_{1/2\beta}$).
- 3- **A gamma phase:** corresponds to the terminal elimination half-life ($t_{1/2\gamma}$).

Structure Activity Relationship of Barbiturates

- 1- At the position 1 (figure 3-14), a substitution by a methyl group causes:
 - a shorter duration of action.
 - convulsions and excitatory phenomenon.

For example: methohexital.

- 2- At the position 2, a substitution by a sulfur atom (thio-) causes:
 - a shorter duration of action.
 - Increased lipid solubility.
 - Increased histamine release.

For example: thiopental.

- 3- At the position 5, an increase of carbon atoms in side chains causes increased hypnotic potency, presence of an aromatic nucleus causes convulsant properties, and presence of a phenyl group causes anticonvulsant properties e.g., phenobarbitone.

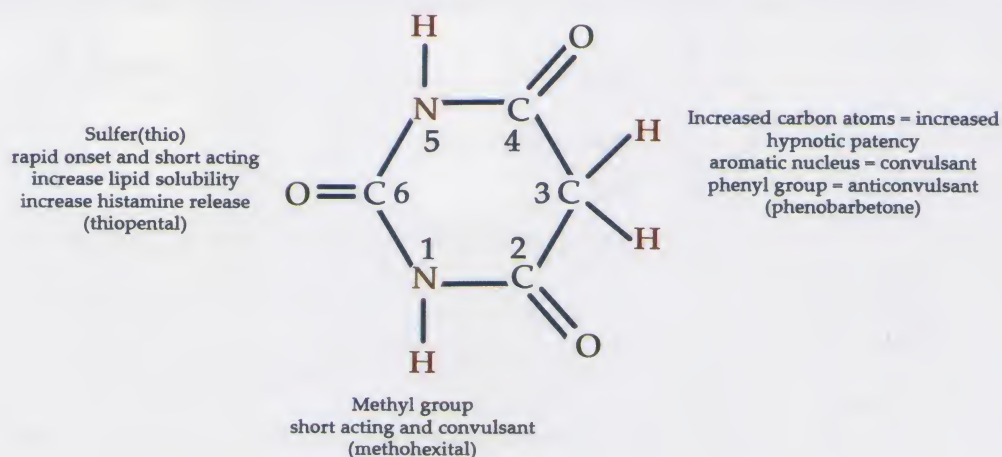


Figure 3-14: A Barbituric acid

Figure 3-15 shows the sites of action of intravenous anesthetics.

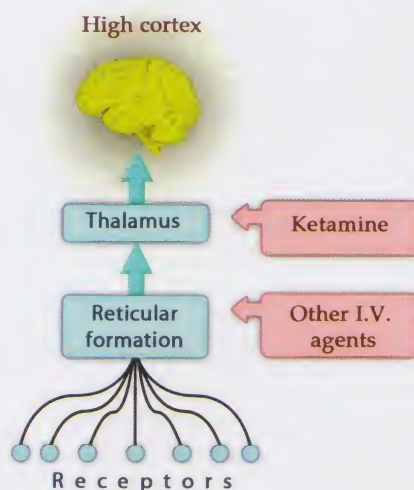


Figure 3-15: Site of action of intravenous anesthetics

Intravenous Anesthetic Agents:

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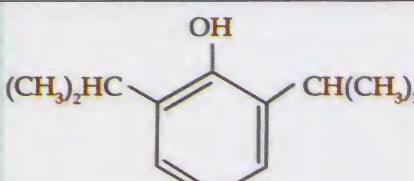
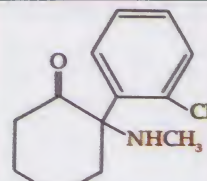
- 1- Barbiturates: - Thiopentone sodium or thiopental (a thio-barbiturate).
- Methohexitone sodium or methohexital (a methyl-barbiturate).
- 2- Sterically hindered alkyl phenols: Propofol (di-isopropyl phenol).
- 3- Carboxylated imidazole compounds: Etomidate.
- 4- Phencyclidine derivatives: Ketamine.
- 5- Benzodiazepines: • Diazepam.
• Midazolam.
• Lorazepam.
- 6- Opioids.
- 7- Neuroleptic agents.
- 8- α_2 -adrenergic agonists: • Clonidine.
• Dexmedetomidine.

Other drugs that not currently available:

- Steroids: • Eltanolone. • Althesin. • Minaxolone.
- Eugenols: Propanidid.

Q: Classify intravenous anesthetic agents according to their chemical structures?

	Thiopental (Intraval)	Etomidate
Chemical structure They have isomers (the most available preparations are racemic i.e., 50% S- and 50% R-).		
Physical properties	<ul style="list-style-type: none"> pH 10.8 (after mixing with saline in the vial). Short shelf life. Water soluble in the vial and lipid soluble inside the body. Formulation: It is stored in nitrogen (to prevent its chemical reaction with the atmospheric CO₂) and mixed with 6% anhydrous Na carbonate (to increase its water solubility). Yellowish powder with a bitter taste and a faint smell of garlic. Vial: 500 or 1000 mg. Freshly prepared solution is stable for 2 weeks, but manufacturers recommend storing for 24 hrs only as it contains no antibacterial preservatives. 	<ul style="list-style-type: none"> pH 6.9 (in the ampoule). Long shelf life. Water soluble in the ampoule and lipid soluble inside the body. Clear aqueous solution containing 35% propylene glycol. Ampoules: 10 mL (2mg/ml) i.e. ampoule contains 20 mg.
Dose i.v. = intravenous route i.m. = intramuscular route.	<p>1- I.v.: (2.5% solution i.e. 25 mg/mL).</p> <ul style="list-style-type: none"> For induction: 3-5 mg/kg For sedation: 0.5-1.5 mg/kg. <p>- The dose varies according to the patient's response, so in healthy adults an initial 4 mg/kg over 15 sec is given; if loss of eye lash reflex does not occur within 30 sec, additional doses of 50-100 mg are only given slowly till loss of consciousness occurs. The 1st 2 mL are given initially, and then the patient is asked if there is any pain to avoid inadvertent intra-arterial injections.</p> <ul style="list-style-type: none"> - In young children 6 mg/kg. - In elderly 2.5-3 mg/kg. <p>2- Rectal: (5-10% solution) 30-40 mg/kg</p> <ul style="list-style-type: none"> - To induce basal narcosis (sleep) in children within 10-15 min. - It may be used to sedate un-cooperative children before anesthesia, but this may cause a loss of airway control. 	<p>1- I.v.</p> <ul style="list-style-type: none"> For induction 0.2 - 0.3 mg/kg.
Pharmacokinetic Distribution	<ul style="list-style-type: none"> Recovery of consciousness: due to redistribution only. Metabolism is responsible for end of drowsiness which may persist for hours (24-36 hrs). Protein binding 80% Non-ionized fraction at physiologic pH 60% t_{1/2α} 2-4 min t_{1/2β} 11 hrs The context-sensitive half-time is long. Solubility: lipid soluble. <p>N.B.: The context sensitive half-time describes the elimination half-time after a continuous infusion. Those with short times can be used for I.v. infusions.</p>	<ul style="list-style-type: none"> Recovery of consciousness due to redistribution. Protein binding: 77% Non-ionized fraction: large. t_{1/2α} 2-4 min t_{1/2β} 3-5.3 hrs The context-sensitive half-time is short. Highly lipid soluble.
Metabolism and excretion	<ul style="list-style-type: none"> In the liver (like all barbiturates except phenobarbitone which is mainly unchanged by the kidneys) by hepatic oxidation to inactive water-soluble metabolites (slower than methohexitone). This causes prolonged drowsiness and disturbed psychomotor function up to 24-36 hrs. Hangover effect and cumulation: is present because repeated doses will saturate the peripheral compartment, so that redistribution cannot occur and the duration of action becomes more dependent on elimination especially in: <ul style="list-style-type: none"> - Elderly patients - Obese patients as doses should be based on the lean body mass as fat distribution is low, however, elimination may be delayed due to increased retention of the drug by the fat. The inactive metabolites are excreted in the urine. Small % is excreted unchanged in the urine. 	<ul style="list-style-type: none"> In the liver (by hepatic microsomal enzymes) and in the plasma (by esterase) by hydrolysis that produces inactive water soluble metabolites. Cumulation: is absent. The inactive metabolites are excreted in the urine and bile. A small % is excreted unchanged in the urine.

Propofol (Deprivan)	Ketamine HCl (Ketamar)
	
<ul style="list-style-type: none"> pH 7 (in the ampoule). Long shelf life. Highly lipid soluble (not water soluble). Formulation: <ul style="list-style-type: none"> It is a white aqueous oil in water emulsion containing Soya bean oil (10%), purified egg phosphatide "egg lecithin" (1.2%) and glycerol (2.25%). In the past, it was formulated in Cremophor El which caused histamine release and anaphylactoid reactions and potentiated muscle relaxants. Other formulation: 1% propofol in 16% poly-oxy-ethylated castor oil, to decrease injection discomfort. Ampoules: 20 ml (10mg/mL) (1%) It should be used completely within 6 hrs of opening the ampoules with good sterile techniques because it contains no antibacterial preservatives; but recently, preservatives have been added as 0.005% di-sodium edentate, or 0.025% sodium meta-bisulfite is added to help retard the rate of growth of micro-organisms (still not FDA approved). 	<ul style="list-style-type: none"> pH 3.5 – 5.5 pKa 7.5 Long shelf life. Extremely lipid soluble (also water soluble). Clear solution containing NaCl to be isotonic. Multi-dose vials: 10mL (50-100 mg/ mL). It contains benzethonium chloride 0.1 mg/mL as a preservative.
<p>1- I.v.: (1% solution i.e. 10 mg/mL).</p> <ul style="list-style-type: none"> For induction: 1.5-2.5 mg/kg. Decrease the dose in elderly and premedicated patients. Increase the dose in children 3-3.5 mg/kg. It is not recommended for children < 3 years old). For anti-emesis: 10-20 mg. <p>2- I.v. infusion:</p> <ul style="list-style-type: none"> For maintenance: multi-step infusion regimen to maintain plasma level at 3-8 µg/ml. 10 mg/kg/hr for the 1st 10 min. 8 mg/kg/hr for the 2nd 10 min. 6 mg/kg/hr for the remaining time. For sedation: to maintain plasma level at 1-2 µg/ml. 2-4 mg/kg/hr e.g. during regional anesthesia or endoscopy or in intensive care. For anti-emesis: 10 µg/kg/min. 	<p>1- I.v.:</p> <ul style="list-style-type: none"> For induction: 1-2 mg/kg Decrease the dose in elderly and shocked patients. Additional doses are needed 1-1.5 mg/kg every 5-10 min. For analgesia (without loss of consciousness) 0.25 – 0.5 mg/kg or 50µg/kg/min. <p>2- I.v. infusion:</p> <ul style="list-style-type: none"> 15-45 µg/kg/min (if with N₂O). 30-90 µg/kg/min (if alone). <p>3. I.m.: 5-10 mg/kg.</p> <p>4. Oral: 5-10 mg/kg.</p> <p>5- Rectal.</p> <p>6- Epidural.</p>
<ul style="list-style-type: none"> Recovery of consciousness due to redistribution and detoxification. Protein binding: 97% t_{1/2α} 2-4 min t_{1/2β} 4 hrs The context-sensitive half-time is short. Solubility: highly lipid soluble. 	<ul style="list-style-type: none"> Recovery of consciousness due to redistribution. Protein binding 12% Non-ionized fraction 60% t_{1/2α} 11-16 min t_{1/2β} 2-4 hrs The context-sensitive half-time is short. Solubility: highly lipid soluble.
<ul style="list-style-type: none"> In the liver and in extra-hepatic sites (as lungs 30%) by conjugation to inactive water soluble metabolites. It is rapid (10 times more than thiopentone), so rapid recovery occurs after continuous infusion. Cumulation: is absent. The inactive metabolites are excreted in the urine. A small % is excreted unchanged in the urine. N.B.: Fospropofol: is a water soluble prodrug that is rapidly hydrolyzed into propofol by alkaline phosphatase which is present in blood but mainly resides in tissues. Fospropofol shows some advantage over propofol which is prepared in lipid based formulations such as Fospropofol is less painful during injection. 	<ul style="list-style-type: none"> In the liver by demethylation and hydroxylation. This produces: <ul style="list-style-type: none"> Active nor-ketamine (1/3-1/5 the potency of ketamine). Other inactive metabolites. Induction of hepatic enzymes may partially explain the development of tolerance in patients who receive multiple doses of ketamine. Cumulation: is absent. The inactive metabolites are excreted in the urine. A small % is excreted unchanged in the urine.

	Thiopental (Intraval)	Etomidate
Pharmacodynamics 1- Central nervous system (CNS) effects - EEG = Electroencephalography - CMRO ₂ = Cerebral metabolic rate for oxygen. - CBF = Cerebral Blood Flow - ICP = Intracerebral Pressure. - CPP = Cerebral Perfusion Pressure.	Mechanism of action: It depresses the reticular formation in the brainstem (see before). 1- CNS depression: ranges from mild sedation up to unconsciousness. • Onset after i.v. bolus: <30 sec, depending on loss of eye lash reflex . Some patients relate a taste sensation of garlic or onion during induction. • Duration after i.v. bolus: 5-10 min, after this time awakening occurs. 2- Potent anticonvulsant effect: EEG changes range from low voltage fast activity (with small doses) up to high voltage slow activity and electrical suppression (with very large doses, repeated boluses, or a continuous infusion). 3- Poor analgesic effect: It has an anti-analgesic effect (by decreasing pain threshold) which occurs at sub-anesthetic blood concentrations i.e. at low doses or during recovery, restlessness in postoperative period may occur. 4- A decrease in CMRO₂: • Cerebral O ₂ consumption decreases (up to 50%). • Vasoconstriction of cerebral vessels that leads to the following: ▫ CBF and ICP decrease. ▫ CPP increases because the decrease in ICP exceeds the increase in arterial blood pressure. CPP = Mean arterial pressure - Cerebral venous pressure or ICP whichever is larger. So, thiopental provides brain protection from transient episodes of focal ischemia e.g., cerebral embolism, or surgical retractors, but not from global ischemia e.g., cardiac arrest. 5- No postoperative nausea or vomiting. 6- No excitatory or emergence phenomenon.	Mechanism of action: It depresses the reticular formation, but unlike barbiturates, it may have dis-inhibitory effect on some parts of CNS that control extra-pyramidal motor activity causing a 30-60% incidence of excitatory phenomenon. 1- CNS depression: • Onset: 30 sec • Duration: 3-8 min 2- It has no anticonvulsant effect: • EEG changes as those associated with barbiturates, but it may activate seizure foci. 3- Very poor analgesic effect Anti-analgesic effect is unknown. 4- A decrease in CMRO₂: • This decreases CBF and ICP (to the same degree as thiopentone). • CPP is well maintained due to minimal cardio-vascular effects, but it is not used in brain protection due to the neuro-toxic effect of propylene glycol. 5- It causes postoperative nausea and vomiting. 6- Excitatory phenomenon (+++) and Emergence phenomenon (+)
2-Respiratory effects	1- Respiratory depression: • It decreases the respiratory rate and tidal volume, but they are increased with surgical stimulation. • It decreases the ventilatory drive to hypercapnia and hypoxia due to a decrease in the sensitivity of the respiratory center. • It produces a short period of apnea frequently preceded by a few deep breaths. • This is more in premedicated patients especially with opioids (as they may need assisted mechanical ventilation). 2- The bronchial muscle tone is increased up to bronchospasm especially in asthmatic patients due to the presence of a sulfur atom. 3- Laryngeal spasm precipitated by surgical stimulation, secretions, foreign bodies (or pharyngeal airway or laryngeal mask) is common in the region of the pharynx or larynx because thiopentone depresses laryngeal reflexes to a lesser extent than other areas of the central nervous system.	1- Respiratory depression: It is the least agent affecting the respiratory system. 2- Bronchial muscle: no effect
3- Cardio-vascular effects	1- Arterial blood pressure: • Is decreased (less than propofol) due to vasomotor center depression which in turn decreases myocardial contractility i.e., negative inotropic action, and produces peripheral vasodilatation especially with large doses or rapid injection. 2- Heart rate: reflex tachycardia occurs due to: - Baroreceptor inhibition caused by hypotension - Inhibition of the vagal tone. 3- Cardiac output: is maintained because of: - Inhibition of baroreceptor reflex that produces vaso-constriction of resistant vessels that slightly increases arterial blood pressure. - Reflex tachycardia N.B.: In absence of adequate baroreceptor reflex i.e. patients cannot compensate for the effects of peripheral vasodilatation e.g., patients with hypovolemia, congestive heart failure, β adrenergic blockade, constrictive pericarditis, cardiac valve stenosis, previously uncontrolled hypertensive patients, or old age; profound hypotension and decreased cardiac output occur.	1- Arterial blood pressure: • Is slightly decreased due to slight peripheral vaso-dilatation (it has no effect on myocardial contractility). 2- Heart rate: No effect 3- Cardiac output: No effect It is the least agent affecting the cardio-vascular system.
4- Neuro-muscular effects	• The muscle tone is decreased at high blood concentrations due to inhibition of spinal cord reflexes. • Muscle movement is common in response to surgical stimulation.	

Propofol (Deprivan)	Ketamine HCl (Ketamar)
<p><u>Mechanism of action:</u> As thiopentone (see before).</p> <p>1- CNS depression: ranges from mild sedation up to unconsciousness.</p> <ul style="list-style-type: none"> Onset after i.v. bolus: 20-40 sec, depending on loss of verbal contact, as transfer of the drug from the blood to the brain is slower than with thiopentone; therefore, a delayed loss of eyelash reflex occurs, so overdosage may occur if this clinical sign is used. Duration after i.v. bolus: 3-8 min. <p>2- Anticonvulsant effect:</p> <ul style="list-style-type: none"> It is unclear. It decreases the duration of seizures induced by electro-convulsive therapy in humans. It decreases the frequency and the amplitude in EEG. Most studies support an anticonvulsant effect of propofol and it may be safely given to patients with seizure disorder. <p>3- Poor analgesic effect and no anti-analgesic effect.</p> <p>4- A decrease in CMRO₂:</p> <ul style="list-style-type: none"> This decreases CBF and ICP. It may cause a critical decrease in CPP < 50 mmHg, but it provides the same degree of cerebral protection during focal ischemia as thiopentone. <p>5- Anti-emetic and anti-pruritic action.</p> <p>6- Excitatory phenomenon (+), but no emergence phenomenon.</p>	<p><u>Mechanism of action</u> It produces dissociative anesthesia or cataleptic state (rather than depression of reticular activating system) i.e. it functionally dissociates the thalamus (which relays sensory impulses from the reticular activating system to the cerebral cortex) from the limbic cortex (which is involved in the awareness of sensation). While some brain neurons are inhibited, others are excited. Clinically, patients appear conscious e.g., eyes opening, swallowing, showing muscle contracture, but are unable to process or respond to sensory input (figure 3-15). It also blocks N-methyl D-aspartate receptors, a subtype of glutamate receptor.</p> <p>1- CNS (+)</p> <ul style="list-style-type: none"> Onset: 30-60 sec after i.v. 15-30 min after i.m. Duration: 10-15 min (i.v.) 15-25 min (i.m.) <p>2- Anticonvulsant effect:</p> <ul style="list-style-type: none"> It is unclear as some researches proved that it has an anticonvulsant effect and may be used in status epilepticus. EEG changes: Loss of alpha rhythm and predominant theta activity. <p>3- Potent analgesic effect at sub-anesthetic blood level. No anti-analgesic effect</p> <p>4- An increase in CMRO₂: This increases cerebral O₂ consumption, CBF and ICP, so it has a harmful effect on patients with space occupying lesions (i.e. no brain protection)</p> <p>5- Postoperative nausea and vomiting</p> <p>6- Emergence phenomenon (++) Excitatory phenomenon (+)</p>
<p>1- Respiratory depression:</p> <ul style="list-style-type: none"> occurs as with thiopentone, with longer periods of apnea. <p>2- It does not affect bronchial muscles.</p> <p>3- Laryngeal spasm is uncommon because it depresses upper airway reflexes (more than thiopentone); therefore, it is the drug of choice with laryngeal masks.</p>	<p>1- Respiration is maintained or slightly stimulated (unless high doses are given).</p> <ul style="list-style-type: none"> Ventilatory drive is minimally affected with ordinary doses. Apnea may occur especially with patients premedicated with opioids. <p>2- Bronchial muscle tone is decreased; it produces potent bronchodilatation.</p> <p>3- Pharyngeal and laryngeal reflexes and patient's airway are maintained, but their presence can not be guaranteed.</p>
<p>1- Arterial blood pressure:</p> <ul style="list-style-type: none"> Is decreased up to 40% (more than thiopentone) due to: Peripheral vasodilatation (mainly) Depressed myocardial contractility. <p>N.B.: Pressor response to tracheal intubation is attenuated to a greater degree than with thiopentone.</p> <p>2- Heart rate: is variable, may be unchanged or markedly decreased down to asystole (very rare) due to: - abolishment of baroreceptor reflex. - central vagal stimulation.</p> <p>3- Cardiac output: is transiently decreased. Arterial blood pressure, heart rate, and cardiac output may be markedly decreased in patients:</p> <ul style="list-style-type: none"> at extremes of age. on negative chronotropic drugs. with reduced intravascular fluid volume. undergoing surgical procedure associated with the oculo-cardiac reflex. who received rapid injection. with impaired left ventricular function. 	<p>There are two actions:</p> <p>Indirect central sympathetic stimulation (predominant) as:</p> <ul style="list-style-type: none"> The arterial blood pressure: is increased up to 20%. The heart rate: is increased up to 20%. The cardiac output: is increased. <p>Therefore, it is beneficial in patients with acute hypovolemic shock (not prolonged severe shock). Also it is avoided in patients with;</p> <ul style="list-style-type: none"> Coronary artery disease. Uncontrolled hypertension. Arterial aneurysm. <p>2- Direct myocardial depressant action:</p> <ul style="list-style-type: none"> It occurs especially in large doses (and in vitro). It is usually masked by the indirect stimulatory action. In patients with sympathetic blockade, e.g., spinal cord transection, exhaustion of catecholamine stores (as severe end-stage shock or heart failure), with sympathetic antagonists or opioids; there is unmasking of the direct inhibitory action with cardiovascular collapse.
<ul style="list-style-type: none"> The muscle tone is decreased at high blood concentrations due to inhibition of spinal cord reflexes. Muscle movement is common with surgical stimulation. 	<ul style="list-style-type: none"> The muscle tone is increased. Spontaneous movement may occur, but reflex movement to surgery is uncommon.

	Thiopental (<i>Intraval</i>)	Etomidate
5- Other effects	<p>1- <u>Renal</u>: It decreases the renal blood flow and in turn, decreases glomerular filtration rate (in proportion to the decrease in the arterial blood pressure).</p> <p>2- <u>Hepatic</u>:</p> <ul style="list-style-type: none"> • It decreases the hepatic blood flow. • It causes induction of hepatic enzymes which increases the rate of metabolism of some drugs as digitalis, steroids, oral anticoagulants, oral contraceptives, and phenytoin. • It combines with cytochrome P-450 enzyme system, interfering with the metabolism of other drugs e.g. tricyclic antidepressants. <p>3- <u>Eye</u>: It decreases the intraocular pressure.</p>	<p>1. <u>Endocrine</u>:</p> <p>Adreno-cortical suppression</p> <ul style="list-style-type: none"> • Due to a dose-dependent inhibition of 11 β-hydroxylase; an enzyme necessary for the conversion of cholesterol to cortisol. • It occurs after a single induction dose (which lasts 4-8 hours) and after long term intravenous infusion (which lasts for more prolonged periods). • This suppression may be: <ul style="list-style-type: none"> - desirable for stress-free anesthesia or, - undesirable, as it prevents useful protective responses against stresses that accompany the peri-operative period and stresses of infections in critically ill intensive care patients.
Adverse effects	<p>1- Central nervous system:</p> <ul style="list-style-type: none"> • Drowsiness persists for 24-36 hours. • Excitatory phenomenon on induction is absent. • Emergence phenomenon on emergence is absent. <p>2- Respiratory depression, bronchospasm, and laryngospasm.</p> <p>3- Cardiovascular depression, profound hypotension and reduced cardiac output in some patients (as above).</p> <p>4- During injection:</p> <p>a- <u>I.v. injections</u> (2.5% solution)</p> <p>Pain and thrombophlebitis especially in small veins or with higher concentrations.</p> <p>b- <u>Peri-vascular injection</u> (extravasations)</p> <p>Tissue necrosis e.g., subcutaneous tissues or median nerve damage in antecubital fossa so, if this occurs, the needle should be left in place and then hyaluronidase and 0.5% lidocaine (5-10 ml) should be injected in the affected tissues to dilute the barbiturate concentrations.</p> <p>c- <u>Intra-arterial injections</u></p> <p>Due to inadvertent injection especially into the brachial artery or an aberrant ulnar artery in the antecubital fossa.</p> <p>Clinical picture:</p> <ul style="list-style-type: none"> • Intense burning pain. • The forearm and hand may become blanched and blisters may appear distally. <p>Mechanism: ischemia and gangrene occur distally due to:</p> <ul style="list-style-type: none"> • Vasoconstriction. • Local release of noradrenaline. • Formation of emboli due to <ul style="list-style-type: none"> - Formation of thiopental crystals in the arterioles. - Endarteritis that may cause thrombosis. - Platelet aggregation because ATP is released from damaged cells. <p>Treatment:</p> <ul style="list-style-type: none"> • Stop injection immediately with any intense pain. • Leave the needle in the artery and inject a vasodilator in it as papaverine 20 mg. • A stellate ganglion block or a brachial plexus block. • I.v. heparin and postoperative oral anticoagulants. <p>5- Allergic reactions:</p> <p>They range from skin rash up to severe anaphylactic (1: 30 000 patients) or anaphylactoid reactions and histamine release (due to the sulfur atom).</p>	<p>1- Central nervous system:</p> <ul style="list-style-type: none"> • Excitatory phenomenon on induction (+++): It is dose related. It is the worst in comparison to other agents. It includes: <ul style="list-style-type: none"> a- Dyskinetic movement which is decreased by premedication with opioid. b- Coughing and hiccup which are decreased by premedication with anticholinergics. • Emergence phenomenon (+) • Postoperative nausea and vomiting (+) 30%. <p>2- Respiratory depression.</p> <p>3- Cardiovascular depression: less than other agents.</p> <p>4- During injection</p> <p>a- <u>I.v. injections</u></p> <p>The worst pain and thrombophlebitis especially in small veins. It is decreased by injection of 10 mg lidocaine shortly before etomidate injection or even mixing the lidocaine in the same syringe</p> <p>b- <u>Peri-venous injections</u> no effect.</p> <p>c- <u>Intra-arterial injections</u> no effect</p> <p>6- Allergic reaction is very rare (1:450 000).</p> <p>7- Adreno-cortical suppression.</p>

Propofol (<i>Deprivan</i>)	Ketamine HCl (<i>Ketamar</i>)
<p>1. Renal: It produces a transient decrease in the renal blood flow.</p> <p>2. Hepatic: It decreases the hepatic blood flow</p> <p>3. Endocrine: It decreases plasma concentration of cortisol.</p>	<p>1. Uterus: It crosses the placenta readily making fetal concentrations of the drug nearly equal to that of the mother.</p> <p>2. Eye: • It transiently increases the intraocular pressure. • Eye movement often persists during the surgical anesthesia stage.</p> <p>3. Salivation is increased, so patients should be premedicated with anticholinergic drugs.</p>
<p>3- Central nervous system:</p> <ul style="list-style-type: none"> • Excitatory phenomenon is present (+). • Emergence phenomenon is absent. <p>2- Respiratory depression.</p> <p>3- Cardiovascular depression (more than other agents).</p> <p>4- During injection:</p> <p>a- Iv. injections More pain occurs especially in small veins. The incidence is decreased if 10 mg lidocaine is given shortly before propofol injection or even if 100 mg lidocaine is mixed in the syringe. No thrombophlebitis</p> <p>b- Peri-venous injections no effect</p> <p>c- Intra-arterial injections no effect</p> <p>5- Allergic reaction: (1:50 000-100 000) It is less than thiopentone.</p> <p>6- Propofol Infusion syndrome (propofol toxicity): It is a rare and fatal condition that occurs in children, especially less than 3 years, if prolonged intravenous propofol infusion is used as in intensive care sedation or prolonged intraoperative propofol infusion in young children.</p> <p>Mechanism:</p> <ul style="list-style-type: none"> • Prolonged infusion of propofol can impair entry of acylcarnitine esters into the mitochondria, interfering with fatty acid oxidation. • Insufficient carbohydrate intake is a precipitating factor because this increases fatty acid catabolism which leads to the propofol infusion syndrome. <p>Clinical picture:</p> <ul style="list-style-type: none"> • Sudden onset of marked bradycardia that is not responding to chronotropes or pacemakers. • Multi-system organ failure: <ul style="list-style-type: none"> - Metabolic acidosis (lactic acidosis). - Hypotension that is not responding to vasopressors. - Heart failure that is not responding to treatment. - Hepatic dysfunction (enlarged with elevated liver enzymes). - Renal impairment up to renal failure. - Bronchospasm. - Coagulopathy. - Occasionally rhabdomyolysis or myoglobinuria. • Lipemic plasma (i.e., hyperlipidemia). <p>Treatment:</p> <p>a- Preventive: propofol is contraindicated in young children (< 3 years) especially in prolonged infusion.</p> <p>b- Curative:</p> <ul style="list-style-type: none"> • Supportive: - Chronotropes up to a pacemaker. - Vasopressors. - Hemodialysis for renal failure. • Active: Charcoal hemoperfusion: It clears propofol efficiently (more than hemodialysis) from the plasma. This leads to immediate improvement of hemodynamics and acid-base status. 	<p>1- Central nervous system:</p> <ul style="list-style-type: none"> • Excitatory phenomenon is present (+). • Emergence phenomenon is present (++) (5- 30%): There is restlessness, delirium, disorientation, agitation, vivid and unpleasant nightmares, out-of-body experience, and hallucination which occur during recovery and up to 24 hrs. Its incidence is decreased by avoidance of verbal and tactile stimulation during the recovery period or by concomitant use of opioid, butyrophenones, benzodiazepines or physostigmine. It is less in children and elderly. • Increased ICP and prolonged recovery. • Postoperative nausea and vomiting (++). <p>2- Respiratory system: no adverse effects.</p> <p>3- Cardiovascular system: Harmful in hypertensive and ischemic heart patients.</p> <p>4- During injection: No effect</p> <p>5- Salivation.</p> <p>6- Skin rash may occur. Hypersensitivity reactions are extremely rare with ketamine (and also with benzodiazepines)</p>

	Thiopental (<i>Intraval</i>)	Etomidate
Indications	1- Induction of anesthesia. 2- Maintenance of anesthesia: It is only suitable for short procedures as cumulation occurs with repeated doses. 3- Basal narcosis by rectal route. 4- Treatment of status epilepticus. 5- During brain protection to decrease ICP.	1. Induction of anesthesia especially for <ul style="list-style-type: none"> • Outpatient anesthesia, but it is replaced now by propofol. • Patients with a compromised cardiovascular system.
Contra-indications a- Absolute	1- Airway obstruction. All i.v. anesthetics should not be given if there is an anticipated difficulty in maintaining an adequate airway. 2- Previous hypersensitivity reactions. 3- Porphyria because it induces amino-levulinic acid synthetase enzyme, which in turn stimulates formation of large amounts of porphyrins (an intermediary in heme synthesis). This precipitates an acute attack of lower motor neuron paralysis or cardiovascular collapse.	1- Airway obstruction. 2- Previous hypersensitivity . 3- Long term infusion. 4- Porphyria. 5- Adrenal insufficiency.
b- Relative contra-indications and precautions	1- Central nervous system: Outpatient anesthesia due to slow recovery and drowsiness. 2- Respiratory system: <ul style="list-style-type: none"> • Bronchial asthma. • Muscle disease e.g. myasthenia gravis or dystrophia myotonica because thiopental administration exaggerates respiratory depression. 3- Cardiovascular system: It is used cautiously (with small doses and slow i.v. injections) in hypovolemia (see before). 4- Renal disease as chronic renal failure . There is a decrease in protein binding. Excretion is not affected so, normal doses can be used, but very slowly . 5- Severe hepatic disease: There is decreased protein binding and impaired metabolism, but this has a little effect on recovery, so normal doses can be used, but very slowly . 6- Obstetrics: Adequate doses must be given to the mother, but excessive doses may cause respiratory and cardiovascular depression in the fetus especially if induction-delivery interval is short. 7- Care should be taken when thiopentone is used in patients with reduced metabolic rates such as those with myxedema, extremes of age, or adreno-cortical insufficiently.	As thiopentone except that it is more suitable for outpatient anesthesia.
Drug interactions	1- Contrast media, sulfonamide, phenylbutazone, and other drugs displace thiopentone from plasma protein binding sites . This increases the free drug which in turn increases systemic side effects. 2- Ethanol, narcotics, antihistamines and other central nervous depressant drugs potentiate the sedative effect of barbiturates . 3- Beta adrenergic blockers potentiate cardiovascular depression of thiopental. 4- It is an enzyme inducer as discussed before.	1- Opioids (as a premedication) decrease the excitatory phenomenon, but delay the recovery; therefore, etomidate is not suitable for outpatient anesthesia. 2- Fentanyl and alfentanil increase the distribution and elimination half-life of etomidate.

Propofol (<i>Deprivan</i>)	Ketamine HCl (<i>Ketamar</i>)
<p>1- Induction of anesthesia especially for outpatient anesthesia.</p> <p>2- Sedation during regional anesthesia, endoscopy, and in the intensive care e.g., during mechanical ventilation.</p> <p>3- Total intravenous anesthesia (TIVA): it is the most suitable agent.</p>	<p>1- Induction of anesthesia especially for:</p> <ul style="list-style-type: none"> • High risk patients (as acutely shocked patients) • Pediatric anesthesia in minor surgeries, investigations (e.g., cardiac catheterization), ophthalmic examinations or radiotherapy. • Difficult locations e.g., sites of accidents and in casualties of wars. • Developing countries: where there is a short supply of anesthetic equipment and trained staff. <p>2- Analgesia e.g. in wound dressing, or positioning of patients with pain before regional anesthesia (e.g., fracture neck femur).</p> <p>3- Treatment of status asthmaticus.</p>
<p>1- Airway obstruction.</p> <p>2- Previous hypersensitivity.</p> <p>3- Long term sedation in children in the intensive care.</p> <p>It is safe in Porphyria.</p>	<p>1- Airway obstruction.</p> <p>2- Porphyria (doubt).</p> <p>3- Increased ICP.</p>
<p>As thiopental except that:</p> <p>1- It is more suitable (than barbiturates) for outpatient anesthesia.</p> <p>2- It is less suitable (than barbiturates) for patients with cardiovascular diseases.</p> <p>3- As induction agents for children < 3 years old.</p> <p>4- As an induction agent in cesarean section due to neonatal suppression.</p> <p>N.B.: History of egg allergy does not necessarily contraindicate the use of propofol because most egg allergies involve reaction to egg white (egg albumin), while egg lecithin is extracted from egg yolk.</p>	<p>1- It is not suitable for outpatient anesthesia due to</p> <ul style="list-style-type: none"> • Prolonged recovery. • Emergence phenomenon. <p>2- It is not suitable for patients with</p> <ul style="list-style-type: none"> • Coronary artery disease. • Uncontrolled hypertension. • Aortic aneurysm. • Sympathetic blockade e.g., spinal cord transection, exhaustion of catecholamine stores (as severe end-stage shock or heart failure), or with sympathetic antagonists or opioids. <p>3- It is not suitable for frequent procedures e.g., frequent radiotherapy due to its prolonged recovery that disturbs sleep and eating pattern on repeated administration.</p> <p>4- It poorly suppresses the response to visceral stimulation, so opioid supplementation is given when visceral stimulation is anticipated.</p>
<p>1- With the previous formulation containing Cremophor EL, it potentiates non-depolarizing muscle relaxants (not with the new formulations).</p> <p>2- Fentanyl and alfentanil concentrations may be increased by a concomitant administration of propofol.</p>	<p>1- Non-depolarizing muscle relaxants potentiate it.</p> <p>2- Theophylline may produce seizures if taken with ketamine.</p> <p>3- Diazepam attenuates ketamine's cardio-stimulatory effects and increases its elimination $t_{1/2}$.</p> <p>4- Sympathetic antagonists as propranolol and phenoxybenzamine unmask the direct myocardial depressant effect of ketamine.</p> <p>5- Lithium prolongs the duration of ketamine.</p> <p>6- Halothane, benzodiazepines or barbiturates decrease the distribution and clearance of ketamine and prolong its action.</p> <p>7- Halothane and other volatile agents potentiate its myocardial depression.</p>

Q: What are the properties of ideal intravenous anesthetics?

Methohexitone Sodium

It is a **methyl barbiturate** that is similar to thiopentone sodium, but has some different features.

- Its **metabolism is 3-4 times more rapid** than thiopental.
- It produces an **epileptic form activity**; therefore, it may be contraindicated in epileptic patients. It is a popular **choice for anesthesia** to facilitate **electroconvulsive therapy** because it does not attenuate the electrical activity of the therapy.
- It produces **excitatory phenomenon**, but not emergence phenomenon.
- It produces **more pain and thrombophlebitis** than thiopentone on injection.

Total Intravenous Anesthesia (TIVA)

Definition:

Total Intra-Venous Anesthesia (TIVA):

It is the use of i.v. anesthetic agents **alone** to produce general anesthesia.

Intra-Venous Anesthesia (IVA):

It is the use of i.v. anesthetic agents + N_2O to produce general anesthesia.

Indications and Advantages:

- 1- It allows **rapid recovery** of consciousness and psychomotor function, especially if propofol is used, when compared to other agents (although new volatile agents as desflurane and sevoflurane produce also rapid recovery).
- 2- It allows **inspiration of a high O_2 concentration** in situations where hypoxemia may occur as one-lung anesthesia, severely ill, or traumatized patients and in severe lung diseases (this avoids the usage of the lungs as a route of uptake of inhalational agents).
- 3- It **avoids the usage of N_2O** e.g., in middle ear surgery, bowel surgery, or increased intracranial pressure.
- 4- It **avoids affection of the hypoxic pulmonary vaso-constrictive reflex** which is adversely affected by volatile agents compared with intravenous agents.
- 5- It is safe in **malignant hyperthermia** (compared with volatile agents).
- 6- It allows **access** as during laryngoscopy or bronchoscopy when delivery of inhalational agents is difficult.
- 7- It is associated with a **lower incidence of nausea and vomiting** (compared with volatile agents).
- 8- It maintains **somato-sensory evoked potential** e.g., in neurological surgeries (compared with volatile agents).
- 9- It **controls intraocular pressure** in ophthalmic surgeries (compared with volatile agents).
- 10- It maintains **anesthesia for acute respiratory distress syndrome (ARDS) patients ventilated with intensive care ventilators**.

Disadvantages:

- 1- It needs a **separate i.v infusion site** (cannula).
- 2- It needs an **infusion device** e.g., infusion pump or syringe pump.
- 3- It is unsuitable for patients with **upper airway obstruction** because TIVA produces rapid loss of airway control; therefore, inhalational induction is preferred with its gradual onset.
- 4- Possibility of **awareness** is high due to the high degree of patient variability in response to drugs.
- 5- **Opioids can cause respiratory depression and muscle rigidity** interfering with ventilation.

Components:

1- Hypnotics: to produce unconsciousness and amnesia.

For example: propofol, ketamine, methohexitone, etomidate, or midazolam.

2- Analgesics: to inhibit reflex response to surgery.

For example: opioids (fentanyl, alfentanil, or sufentanil).

3- Muscle relaxants: to provide muscle relaxation, for example: atracurium, cis-atracurium, or pancuronium.

4- O_2 enriched air.

The details of each component should be discussed.

Monitoring during TIVA:

Beside the usual monitors used in the anesthesia, the depth of anesthesia should be assessed during TIVA due to the high possibility of awareness. These neurological monitors include:

- 1- Clinical signs such as movements, changes in heart rate, arterial blood pressure, and breathing.
- 2- Spontaneous electromyography (EMG).
- 3- Electroencephalography (EEG).
- 4- Esophageal contractility.
- 5- Mid-latency auditory evoked potentials.
- 6- Bi-spectral monitor.

The details of these monitors are discussed in the chapter of "Basic Physics for Anesthesia & Intensive Care".

Techniques:

1. Intermittent Injections:

- It is acceptable only for procedures of short duration in unparalyzed patients because the plasma concentration of the drug and the anesthetic effect vary widely.

2. Manual Infusion Techniques:

- The infusion rate required to achieve a predetermined target plasma concentration of an i.v. drug can be calculated by:

Infusion rate ($\mu\text{g}/\text{min}$) = Steady state plasma concentration ($\mu\text{g}/\text{mL}$) \times clearance (mL/min), but actually clearance is variable from one patient to another, so it is difficult to calculate the infusion rate (figure 3-16).

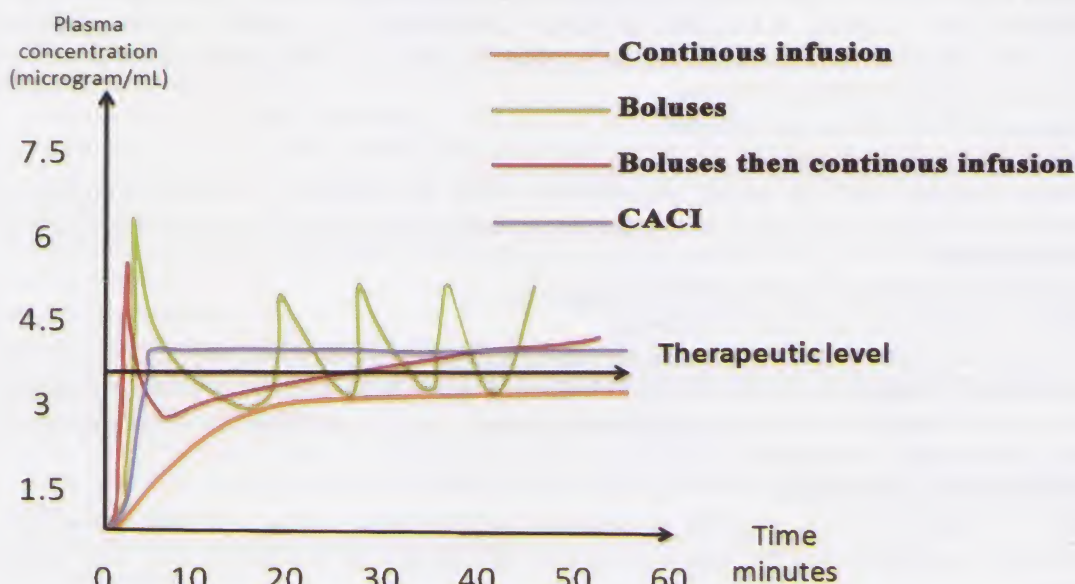


Figure 3-16: Plasma concentration with different methods of administration

There are many ways for manual infusion:

a. A constant infusion:

- It is not suitable because the serum concentration of the drug increases slowly **taking 4-5 times the elimination half-life ($t_{1/2\beta}$)** of the drug to reach the steady state.

b. A bolus injection followed by a constant infusion:

- It causes excessive concentration initially (with an increase in the incidence of side effects) i.e. the target concentration is initially exceeded, which is followed by a prolonged dip below the target concentration.

c. Multi-step infusion regimen:

It is commonly used with propofol as follows:

Bolus dose	1 mg/kg.
then	10 mg /kg/hr for the 1 st 10 min
then	8 mg/kg/hr for the 2 nd 10 min
then	6 mg/kg/hr for the remaining time.

This allows, on average, the target plasma concentration to be reached (about 3 $\mu\text{g}/\text{mL}$), allowing satisfactory anesthesia in unparalyzed patients who receive N_2O and fentanyl. Higher infusion rates are needed if N_2O and fentanyl are not used.

3. Target Controlled Infusion System (TCI System) or Computer-Assisted Continuous Infusion (CACI):

Idea:

• The system delivers the required amount of a drug to achieve a **target blood concentration** of the drug for a given patient. This **amount is calculated**, several times per minute, **by a computer** with a program that incorporates **the pharmacokinetic data and other variables such as the patient's weight, gender, and age**. After that, the system calculates the **appropriate infusion rate** of the drug required to produce the preset target plasma concentration which is selected by the anesthesiologist.

In other words, the drug is infused by a syringe driver which is under control of a computer.

• At first, the syringe driver infuses the drug very rapidly (as a slow bolus) and then delivers the drug at a progressively decreasing infusion rate.

If the anesthesiologist selects to decrease the target plasma concentration of the drug, the syringe driver; under control of the computer; stops the infusion until the computer calculates that the target concentration is reached and then infuses the drug at an appropriate rate to maintain a constant level. The reverse occurs if a smaller target concentration is selected i.e., **the anesthesiologist is required only to enter the desired target concentration** and to change it when clinically indicated, in the same way as a vaporizer might be manipulated according to the clinical signs of anesthesia.

Examples:

• **Propofol** is the most common drug used in the TCI system which is called **Diprifusor system**. It is the only commercially available TCI system. It has an identification tag which enables the Diprifusor to recognize the drug and concentration in the prefilled syringe and also prevents reuse of syringes by disabling the magnetic pattern in the tag.

• **Remifentanyl TCI** is still under research.

The Target Plasma Concentration:

TCI system assumes that the patient is conscious when the infusion is started. Consequently, it is inappropriate to connect and start a TCI system in a patient who is already unconscious, as this causes an initial overdosage.

• For induction of anesthesia (while 100% O₂ is given):

4-6 µg/mL is chosen in the majority of patients.

A time is needed for the system to increase the rate of infusion towards the target plasma concentration.

- A higher target **6-8 µg/mL** is chosen if a **rapid induction** is needed especially in **young fit patients**.

- A lower target **1-2 µg/mL** is chosen for **high-risk patients**, which is **increased in small steps (0.5-1 µg/mL)** until the desired effect is reached.

• For maintenance of anesthesia:

3-6 µg/mL is required in the majority of patients, but **the exact value will depend on** the patient, premedication, analgesia, and the degree of surgical stimulation (it is adjusted according to **the clinical situation**).

- Lower target concentrations are needed (by about 1/3), if opioids and/or nitrous oxide are used simultaneously.

- The **effective concentration (the EC₅₀) or the minimum target concentration of propofol** that is required to prevent movement in 50% of patients in response to a painful stimulus (i.e., surgical incision) is:

6-7 µg/mL when patients are on **O₂ enriched air**, and

4-5 µg/mL when patients are on **O₂ and 67% N₂O**.

It is equivalent to the MAC.

• For sedation:

0.5-2.5 µg/mL is needed in most patients.

Advantages (over other TIVA methods):

1- Simplicity:

2- The rapidity with which plasma concentrations can be changed (especially upwards).

3- Avoidance of the need for the anesthesiologist to undertake any calculations; therefore, errors are avoided.

Disadvantages:

1- It is **relatively inaccurate** because the actual concentration achieved may be > 50% greater than or less than the predicted concentration. This is not a major practical disadvantage assuming that the anesthesiologists adjust the target concentration according to clinical signs related to the adequacy of anesthesia.

2- It is used **only for patients over the age of 16 years** as the program that deals with the pharmacokinetics of ages less than 16 is not yet available commercially.

3- It needs an **intravenous line not less than 20 G** to allow the syringe driver to work properly which is sometimes not available.

Closed-Loop System:

• TCI systems may be used as a part of a closed-loop system to control depth of anesthesia. Because there is no available method of measuring blood concentrations of intravenous anesthetics on-line, it is necessary to use some types of monitors of depth of anesthesia such as the auditory evoked potentials, or a bi-spectral system (BSI) on the input side of the system.

• In the future, an intelligent infusion pump may be designed where a robotic-like system can interpret the level of the depth of anesthesia (detected by e.g., BSI) and adjust the TCI to maintain the depth of anesthesia at a constant level.

Melatonergic Drugs

It was discovered by **Mohammed Naguib**, a Professor of Anesthesia.

Melatonin is **N-acetyl-5-methoxy tryptamine** which is normally secreted **from the pineal body**.

Action: It plays an important role in:

- Setting the correct timing of sleep-awake cycles in mammals.
- Regulating circadian rhythm.
- Controlling the reproductive axis.
- Enhancing the immune system.
- Anticonvulsant and antioxidant activities.

It acts on melatonin receptors subtypes MT_1 and MT_2 that act via G_i proteins associated with inhibition of adenylyl cyclase enzyme.

Role in Anesthesia:

It acts as **hypnotic-anesthetic agent** due to its hypnotic, anticonvulsant and anti-nociceptive properties.

Therefore, it is used as:

➤ A premedication agent:

- Sublingual melatonin 0.05, 0.1, or 0.2 mg/kg.
- It produces preoperative anxiolysis and sedation without impairment of psychomotor skills or affecting the quality of recovery.
- It has the following advantages over benzodiazepines e.g. midazolam:
 - Benzodiazepines decrease the duration of rapid eye movement (REM) sleep thus negatively affect sleep quality.
 - Benzodiazepines induce hangover effects.

➤ An induction agent:

- It produces dose-dependent hypnotic effects similar to that seen with thiopental and propofol (i.e., the same processed EEG pattern), but less potent.

Bromo-melatonin:

A brominated analog, 2-bromo-melatonin, is produced where substitution with the bromine occurs at the 2-indole position of N-acetyl-5-methoxy tryptamine (melatonin). It has the following advantages:

- It has **more hypnotic and analgesic actions (5 times more potent than melatonin)**.
- It has the **same rapid onset and short duration of propofol** in equipotent doses, but its **analgesic effect persists for a longer period**.

OPIOID (NARCOTIC) ANALGESICS

The term “**opioid**” refers to all drugs, both **synthetic and natural**, that act on opioid receptors.

The term “**opiate**” refers to **only naturally occurring** opioids derived from the opium poppy *papaver somniferum* (figure 3-17).



Figure 3-17: The opium poppy *papaver somniferum*

Classification

a) Pure Opioid Agonists: They produce dose-dependant agonist activity at opioid receptors and produce the maximum effect.

1- Natural Opium Alkaloids (Opiates):

- **Phenanthrenes:** - Morphine.
 - Codeine (methyl morphine).
 - Papavertum (a mixture of morphine, codeine, and papaverine).
- **Benzyloisoquinolines:** - Noscapine.
 - Papaverine.

2- Semi-Synthetic Opium Alkaloids:

- **Phenanthrenes:** - Dia-morphine or diacetylmorphine (heroin).
 - Oxymorphone.
 - Hydromorphone.
 - Oxycodone.
 - Dihydrocodone.

3- Synthetic Opioids: (Most of them act as agonists on μ receptors)

- **Phenylpiperidines:** - Meperidine (pethidine).
 - Fentanyl.
 - Alfentanil.
 - Sufentanil
 - Remifentanyl (the only one that contains ester linkage).
- **Diphenyl-propylamines:** - Methadone.
 - Dextro-propoxyphene.

N.B.: Tramadol (*Tramal*) is a non-opioid analgesic drug.

b) Partial Opioid Agonists:

- They **bind to mu (μ) receptors** with high affinity, but they have a **limited partial response** and efficacy (i.e., not able to produce maximal biological effects). They also often exert a partial agonist action at other receptors, including kappa (κ) and delta (δ) receptors.
- At low doses, they antagonize previous pure opioid induced analgesia; therefore, if other opioids are used intraoperatively, they should not be used postoperatively; otherwise, reversal of analgesia occurs. At high doses, they produce analgesia and respiratory depression with a **ceiling (plateau) effect** whatever the dose is.
- Buprenorphine (*Temgesic*): is the only one available; it is derived from the opium alkaloid thebaine.

2) Opioid Agonist/Antagonists:

- They **bind to mu (μ) receptors**, but produce **no effect (i.e. antagonism)**.

They also often exert **an agonist action** at other receptors, including kappa (κ) and delta (δ) receptors.

- They produce analgesia and respiratory depression with a **ceiling (plateau) effect** whatever the dose is.

They include - Pentazocine (*Sosegon*).

- Butorphanol (*Stadol*).
- Nalbuphine (*Nubain*).
- Nalorphine.
- Levorphanol (*Dormoran*).

3) Pure Opioid Antagonists:

- They **bind to mu (μ) receptors**, but produce **no effect (i.e. antagonism)**. They do not have any agonist action.

- They include - Naloxone (*Narcan*).

- Naltrexone (*ReVia*).
- Nalmephen (*Revex*).

They act on central and peripheral receptors.

- Methyl naltrexone
- Alvimopan.

The latter two drugs act on peripheral receptors only.

Structure-Activity Relationship

Structural modification affects agonist activity and alters physiochemical properties.

Levo-isomers are the most **active form** in many opioids e.g., levo-morphine.

For example:

- **Potency**: is increased by:

- Presence of **tertiary nitrogen**, which is important for crossing the blood brain barrier and for potency, while presence of quaternary nitrogen decreases the ability of crossing of the blood brain barrier.
- Hydroxylation of C-3 phenol group or C-14.
- Oxidation of C-6 e.g., hydromorphone.
- Double acetylation of C-3 and C-6 e.g., diamorphine.
- Reducing the double bond at C-7/8.

- **Antagonism** occurs as follows:

- A short-chain alkyl substitution produces a mixed agonist-antagonist.
- Removal or substitution of the methyl group on the nitrogen produces an antagonist.
- Hydroxylation or bromination of C-14 produces a full antagonist.

Pharmacokinetics

Absorption:

It depends on the route. This is discussed in details in the chapter of pain management.

Distribution:

- It depends on lipid solubility, the non-ionized fraction, and protein binding (for values, see the tables later).
- Significant amounts of lipid-soluble opioids can be **retained by the lungs (first-pass uptake)**, reducing the initial peak plasma concentration, and diffuse back later into the systemic circulation.
- **Redistribution terminates the action of small doses** of all of these drugs, whereas **larger doses** must depend on **bio-transformation** to adequately lower plasma levels.
- Highly lipid-soluble opioids especially fentanyl have a late second peak of plasma level up to 4 hours after the last intravenous dose. This is because the drug is sequestered in gastric juice and then reabsorbed from the small intestine due to its high lipid solubility.

Metabolism and Excretion:

See the tables later.

Pharmacodynamics

Mechanism of Action:

a) In the Brain:

- Opioids excite neurons in peri-aqueductal grey matter (PAG) and in the nucleus reticularis paragiganto-cellularis (NRPG) causing stimulation of nucleus raphe magnus (NRM).
- From the latter, serotonin (5-HT) and enkephalin containing neurons run to substantia gelatinosa of the dorsal horn causing an inhibitory effect on transmission.

b) In the Spinal Sites:

- Opioids also act directly on the dorsal horn.
- Locus caeruleus (LC) sends norepinephrine neurons which inhibit the dorsal horn (figure 3-18).

Opioid receptors:

Receptor Classification		Clinical Effects	Agonists	Antagonists
Recent	Old			
MOP	Mu (μ) or OP3	<ul style="list-style-type: none"> • μ1: high affinity <ol style="list-style-type: none"> 1. Central supraspinal analgesia 2. Spinal analgesia 3. Euphoria 4. Miosis 5. Bradycardia. 6. Muscle rigidity 7. Hypothermia 8. Urine retention. • μ2: low affinity <ol style="list-style-type: none"> 1. Spinal analgesia. 2. Respiratory depression 3. Gut inhibition and constipation. 4. Physical dependence 	<ul style="list-style-type: none"> - Met-enkephalin - Beta (β)-endorphin - Dynorphin - Morphine - Meperidine - Fentanyl - Sufentanil - Buprenorphine (partial agonist) 	<ul style="list-style-type: none"> - Pentazocine - Nalbuphine - Naloxone - Naltrexone - Nalmefene
KOP	Kappa (κ) or OP1	<ol style="list-style-type: none"> 1. Central supraspinal analgesia 2. Spinal analgesia 3. Sedation and dysphoria 4. Miosis 5. Respiratory depression 	<ul style="list-style-type: none"> - Beta (β)-endorphin - Dynorphin - Morphine - Pentazocine - Nalbuphine 	<ul style="list-style-type: none"> - Naloxone
DOP	Delta (δ) or OP2	<ol style="list-style-type: none"> 1. Central supraspinal analgesia (in high doses only) 2. Spinal analgesia 3. Dependence 4. Gut inhibition and constipation 5. Behavioral changes 6. Epileptogenic action 7. Urine retention 	<ul style="list-style-type: none"> - Met-enkephalin - Leu-enkephalin - Beta (β)-endorphin - Morphine 	<ul style="list-style-type: none"> - Naloxone
NOP	Sigma (σ) or Nociceptin (Orphanin FQ peptide receptor)	<ol style="list-style-type: none"> 1. Vasomotor center stimulation 2. Dysphoria and hallucination 3. Mydriasis 4. Respiratory stimulation 	<ul style="list-style-type: none"> - Pentazocine - Nalbuphine - Nalorphine - Ketamine - Nociceptin (orphanin FQ) 	<ul style="list-style-type: none"> - It is considered an opioid-like receptor, not a true opioid receptor as it is not reversed by Naloxone.

Epsilon (ϵ): is a recently discovered receptor.

Opioid receptors have also been isolated from somatic and sympathetic peripheral neurons and may decrease pain peripherally via MOP receptors.

Molecular Mechanism

Opioid receptors, MOP and DOP, act via **G inhibitory protein (Gi)** which in turn:

- inhibits adenyl cyclase.
- stimulates K^+ channel opening. This **increases K^+ efflux** that produces **hyper-polarization** of the cell membrane.

KOP opioid receptors act via **inhibition of voltage dependent N-type Ca^{++} channels**

Both mechanisms above decrease the presynaptic release of excitatory neurotransmitters (e.g., acetylcholine, dopamine, norepinephrine, glutamate and substance P).

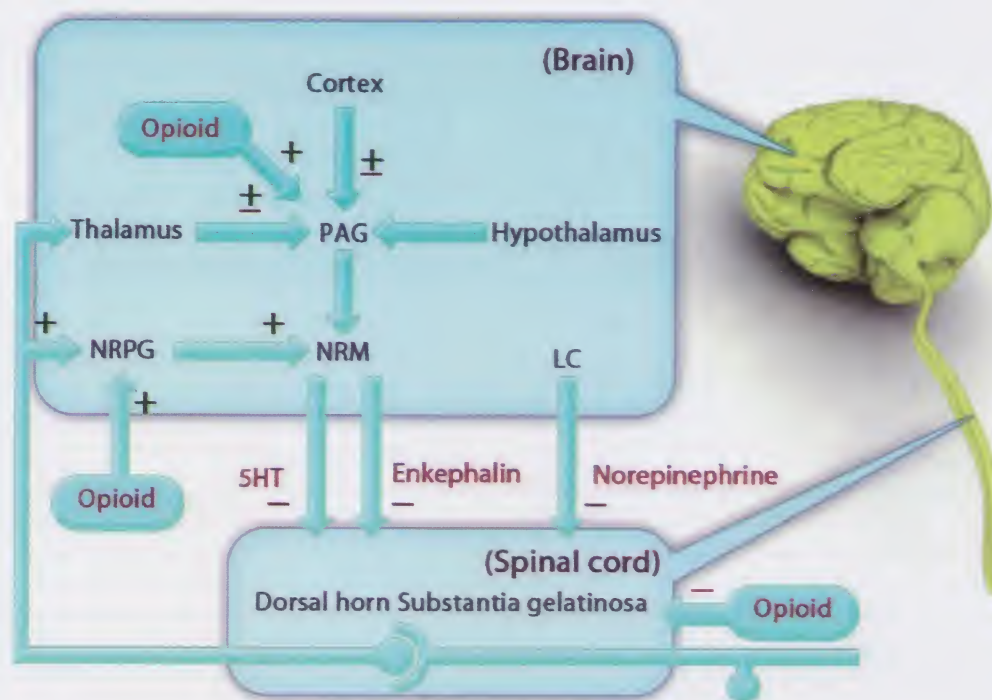


Figure 3-18: Mechanism of action of opioids

Individual Opioids

The most common used opioids include:

- 1- Morphine.
- 2- Meperidine (pethidine).
- 3- Fentanyl.
- 4- Alfentanil.
- 5- Sufentanil.
- 6- Remifentanyl.

They are discussed in the tables later.

7- Diamorphine (Diacetylmorphine) (Heroin):

It is similar to morphine except that:

- It is a semi-synthetic agonist related to morphine.
- It is a **prodrug**; it is inactive at opioid receptors, but it is converted in the liver by rapid acetylation into active metabolites such as 6-monoacetylmorphine, morphine, and morphine 6-glucuronide.
- It is **more lipid soluble** than morphine; therefore, **twice potent** as morphine and produces more euphoria.
- It is more suitable for palliative use (cancer pain), when high concentrations are needed in relatively low volumes.
- It is available for parenteral and oral use.

Other individual opioids:

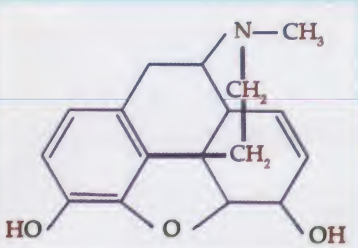
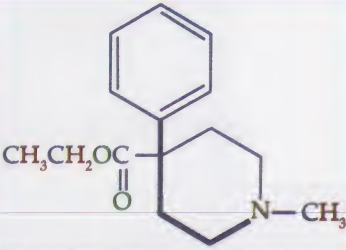
They are discussed in the chapter of pain management.

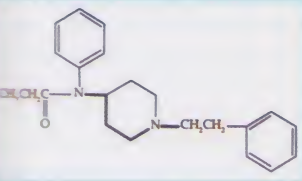
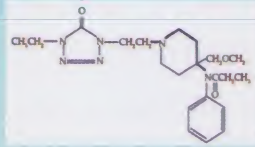
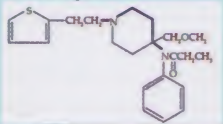
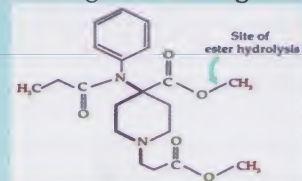
Patient controlled analgesia.

Spinal (epidural or intrathecal) opioids.

Peripheral opioid antagonist.

These subjects are discussed in chapter of "Pain Management".

	Morphine	Meperidine (Pethidine)
Chemical structure	<ul style="list-style-type: none"> It is a natural opium alkaloid, pure agonist, tertiary amine, and weak base. Although it is possible to synthesize, it is produced commercially from the dried juice of the seed capsules of the opium poppy <i>papaver somniferum</i>. 	<ul style="list-style-type: none"> It is a synthetic pure agonist. 
Pharmacokinetics	<p>pKa: 7.9</p> <p><u>Lipid solubility:</u> (+) → slow onset.</p> <p><u>Duration:</u> 3-5 hours after i.v. or i.m. (it usually lasts more due to presence of an active metabolite).</p> <p><u>Peak effect:</u> 15-20 min after i.v. and 60-90 min after i.m.</p> <p><u>Half-lives:</u> (for definitions see before).</p> <ul style="list-style-type: none"> $t_{1/2\alpha}$ = 25min. $t_{1/2\beta}$ = 3.5 hours. <p>• Context-sensitive half-life: is prolonged.</p> <p><u>Protein binding:</u> (++) 35%.</p> <p><u>Non-ionized fraction:</u> (++) 23%.</p> <p><u>Metabolism:</u></p> <ul style="list-style-type: none"> It occurs mainly in the liver by N-dealkylation, oxidation and conjugation with glucuronides. Morphine-3-glucuronide and morphine-6-glucuronide are formed, the latter is active (more potent, and has a longer duration than morphine; therefore, the clinical effect may exceed that expected from $t_{1/2\beta}$, especially in renal impairment, as this metabolite is excreted via the kidney). It may also occur in extra-hepatic sites as kidney and gastrointestinal tract. There is a high 1st pass effect (70%) in the gut wall and liver. This causes low bioavailability after oral route, (30%), so relatively higher doses are needed. At the same time, morphine-6-glucuronide production is greater with oral than i.v. and i.m. routes, making the oral morphine dose effective. <p><u>Excretion:</u></p> <ul style="list-style-type: none"> A large % is excreted as water soluble end products by the kidney. 5-10% is excreted unchanged by the kidney. <p>So, in renal impairment, there is prolonged duration of action.</p> <ul style="list-style-type: none"> 10% is excreted unchanged by the bile, stool, saliva, sweat and milk. 	<p>pKa: 8.5</p> <p><u>Lipid solubility:</u> (++) → more rapid onset than morphine.</p> <p><u>Duration:</u> 2-3 hours</p> <p><u>Half-lives:</u></p> <ul style="list-style-type: none"> $t_{1/2\alpha}$ = 8min. $t_{1/2\beta}$ = 3-5 hours. <p>• Context-sensitive half-life: is prolonged.</p> <p><u>Protein binding:</u> (+++) 70%</p> <p><u>Non-ionized fraction:</u> (+) 7%</p> <p><u>Metabolism:</u></p> <ul style="list-style-type: none"> It occurs in the liver by N-demethylation. One of the metabolites is active and called normeperidine (norpethidine). Its accumulation causes convulsions especially in renal impairment (which is not reversed by naloxone). <p><u>Excretion:</u></p> <ul style="list-style-type: none"> A large % is excreted as active end products by the kidney, so in renal failure, normeperidine may lead to convulsions. 5-10% is excreted unchanged by the kidney and bile.
Actions, side effects, and contra-indications	<p><u>Potency:</u> It is the gold standard against which all other opioids are judged.</p> <p><u>1) Analgesia:</u></p> <ul style="list-style-type: none"> Especially for - Somatic and visceral types of pain. - Dull and continuous rather than sharp and intermittent pain. <p>• Mechanism: see before.</p> <p>It also decreases psychological and emotional components of pain.</p> <ul style="list-style-type: none"> Analgesic action is augmented by euphoria. With increasing the dose, drowsiness, sleep, and finally anesthesia can occur. 	<p><u>Potency:</u> 1/10 of morphine.</p> <p><u>1) Analgesia:</u></p> <p>As morphine.</p>

Fentanyl	Alfentanil	Sufentanil	Remifentanyl
<ul style="list-style-type: none"> Synthetic pure agonist at μ receptors. It is related structurally to meperidine. 	<ul style="list-style-type: none"> Synthetic pure agonist at μ receptors It is related structurally to fentanyl. 	<ul style="list-style-type: none"> Synthetic pure agonist at μ receptors. It is related structurally to fentanyl. 	<ul style="list-style-type: none"> Synthetic pure agonist at μ receptors It is the only opioid containing ester linkage. 
<p>pKa: 8.4</p> <p><u>Lipid solubility:</u> (++++)\rightarrow very rapid onset; within 1-2 min with the i.v. route.</p> <p><u>Duration:</u></p> <ul style="list-style-type: none"> 20-60 min after single bolus due to redistribution. 2-5 hours after high dose or infusion (up to 9 hours in elderly due to decreased elimination). <p><u>Half-lives:</u></p> <ul style="list-style-type: none"> $t_{1/2\alpha} = 3$ min $t_{1/2\beta} = 2-4$ hours. Context-sensitive half-life: 4.3 hours. <p><u>Protein binding:</u> (++) 90%.</p> <p><u>Non-ionized fraction:</u> (+) 8.5%</p> <p><u>Metabolism:</u></p> <ul style="list-style-type: none"> It occurs mainly in the liver by N-dealkylation resulting in inactive metabolites. There is a high 1st pass effect (70%) in the gut wall and liver. Therefore, it is not given orally. <p><u>Excretion:</u></p> <ul style="list-style-type: none"> A large % is excreted as water soluble end products by the kidney. A small % is excreted unchanged by the kidney and bile. 	<p>pKa: 6.5</p> <p><u>Lipid solubility:</u> (+++)\rightarrow The most rapid onset (one arm to brain circulation time) with the i.v. route.</p> <p><u>Duration:</u></p> <ul style="list-style-type: none"> 10-25 min <p><u>Half-lives:</u></p> <ul style="list-style-type: none"> $t_{1/2\alpha} = 2$ min $t_{1/2\beta} = 1.5$ hour. Context-sensitive half-life: 1 hour. <p><u>Protein binding:</u> (++++) 91%.</p> <p><u>Non-ionized fraction:</u> (++++) 89%.</p> <p>N.B: Although it is less lipid soluble than fentanyl, it has a more rapid onset and a shorter duration because:</p> <ul style="list-style-type: none"> It has the highest non-ionized fraction at physiologic pH. It has a small volume of distribution. <p><u>Metabolism:</u> As fentanyl.</p> <p><u>Excretion:</u> As fentanyl.</p>	<p>pKa: 8</p> <p><u>Lipid solubility:</u> (++++)\rightarrow very rapid onset, more than fentanyl.</p> <p><u>Duration:</u></p> <ul style="list-style-type: none"> 40-50 min after single bolus (slightly shorter than fentanyl). <p><u>Half-lives:</u></p> <ul style="list-style-type: none"> $t_{1/2\alpha} = 1$ min $t_{1/2\beta} = 2.5$ hours. Context-sensitive half-life: 30 min. <p><u>Protein binding:</u> (++++) 93%.</p> <p><u>Non-ionized fraction:</u> (++) 20%.</p> <p><u>Metabolism:</u> As fentanyl, but one of its metabolites called des-methylfentanyl is active at MOP receptors (10% of potency of sufentanil).</p> <p><u>Excretion:</u> As fentanyl.</p>	<p>pKa: 7.3</p> <p><u>Lipid solubility:</u> (++)\rightarrow very rapid onset.</p> <p><u>Duration:</u></p> <ul style="list-style-type: none"> 2-5 min (ultra-short) due to rapid metabolism and not due to redistribution. <p><u>Half-lives:</u></p> <ul style="list-style-type: none"> $t_{1/2\alpha} = 1.3$ min $t_{1/2\beta} = 9.5$ min. Context-sensitive half-life: 3-5 min. regardless of the duration of the infusion; therefore, no drug accumulation occurs even after repeated doses or prolonged infusion (but in all other opioids, it is increased). <p><u>Protein binding:</u> (++) 70%.</p> <p><u>Non-ionized fraction:</u> (++) 58%.</p> <p><u>Metabolism:</u> It is rapidly hydrolyzed by non-specific red cell, plasma, and tissue esterases (as esmolol) because it contains ester linkage. These enzymes are different from plasma cholinesterase; therefore, its duration is not affected by renal or hepatic diseases, or plasma cholinesterase deficiency.</p>
<p>100 times more potent than morphine</p> <p><u>1) Analgesia:</u> As morphine.</p>	<p>20 times more potent than morphine.</p> <p>It is similar to fentanyl action except that:</p>	<p>600 times more potent than morphine.</p> <p>It is similar to fentanyl action.</p>	<p>100 times more potent than morphine.</p> <p><u>1) Analgesia:</u> It is used mainly intra-operatively to:</p> <ul style="list-style-type: none"> supplement general anesthesia as it helps decreasing the doses of volatile and i.v anesthetics. be a part of i.v. sedation. allow rapid recovery when needed as in day case anesthesia and wake-up test in neurosurgery.

Morphine	Meperidine (Pethidine)
<p>2) Central nervous effects:</p> <ul style="list-style-type: none"> • All opioids decrease CMRO₂, CBF, and ICP due to cerebral vaso-constrictive effect, but to a much lesser extent than barbiturates or benzodiazepines. • All opioids tend to produce a mild decrease in the mean arterial pressure, but more than the decrease of ICP, so CPP may fall slightly especially in patients with abnormal intracranial elastance. • All opioids have no effect on cerebral autoregulation. • Sedation occurs; it is contraindicated in myxedema as these patients are more sensitive. • Euphoria and hallucination may occur especially in addicts and if there is pain. Dysphoria (i.e., mental discomfort, restlessness and malaise) may occur especially in normal subjects with no pain. • Convulsions on high doses may occur; therefore, it is contraindicated in epilepsy due to decreased GABA release. • Electroencephalography (EEG): All opioids produce a progressive decrease in EEG frequency, but in high doses they may produce δ-waves. Burst suppression is not seen even with high doses. • Tolerance, physical dependence, addiction and withdrawal symptoms may occur. <p>3) Respiratory effects:</p> <ul style="list-style-type: none"> • It inhibits the respiratory center directly which results in a decrease in the respiratory rate and tidal volume within 2-5min after i.v. administration. High doses may produce apnea, but the patient remains conscious and able to initiate a breath if asked to do so. • There is a decrease in CO₂ response to ventilation. The apneic threshold (the highest PaCO₂ at which a patient remains apneic) is elevated. Depressed ventilation may elevate CO₂, resulting in cerebral vasodilatation and increased ICP. Therefore, it is contraindicated in: <ul style="list-style-type: none"> • Pulmonary diseases as emphysema or cor pulmonale. • Increased ICP as head injury. • Hypoxic drive is decreased. • It inhibits the cough reflex (i.e., an antitussive action). <p>4) Cardiovascular effects:</p> <ul style="list-style-type: none"> • Heart rate: It is occasionally decreased due to vagal center stimulation. • Arterial blood pressure: It is usually maintained and minimally affected in normal supine patients, but it is decreased in: - Hypovolemic patients. <ul style="list-style-type: none"> - Patients on vasodilators. - Rapid changing from supine to standing positions (i.e., orthostatic hypotension). <p>Due to: - Inhibition of vasomotor center that results in peripheral vasodilatation. - Blunting of sympathetic reflexes. - Histamine release.</p> <p>Therefore, it is contraindicated in these patients.</p> <ul style="list-style-type: none"> • All opioids are effective in suppressing the stress response to laryngoscopy and intubation. <p>5) Nausea and vomiting:</p> <ul style="list-style-type: none"> • They occur some hours after administration and persist for 6-8 hours. • They are the most common postoperative complaint. • They are similar to other opioids in equianalgesic doses. • Due to • stimulation of dopamine receptors (due to dopamine-like action) of the chemoreceptor trigger zone, so dopamine antagonists e.g., butyrophenones and phenothiazines are effective as antiemetics in opioid-induced vomiting. <ul style="list-style-type: none"> • Vestibular component, so ambulant patients suffer more. <p>6) Histamine release: is common and results in:</p> <ul style="list-style-type: none"> • Erythema and pruritis at site of injection. • Hypotension. • Warm and flush sensation. • Bronchospasm, so it is contraindicated in bronchial asthma. 	<p>2) Central nervous effects: As morphine except that:</p> <ul style="list-style-type: none"> • Less euphoria is produced. • Convulsions, hyperexcitability, and increased EEG activity may occur in toxic doses due to accumulation of normeperidine. • Effective treatment of postoperative shivering is produced by a small dose of meperidine; 25 mg; due to an unknown mechanism, but KOP receptor activation may play a role (it is superior over other opioids in the management). <p>3) Respiratory effects:</p> <ul style="list-style-type: none"> • It inhibits respiratory center directly to the same degree as morphine in equipotent doses. • There is no action on cough reflex. <p>4) Cardiovascular effects:</p> <ul style="list-style-type: none"> • Heart rate: it is increased due to the anti-cholinergic (atropine-like) action because its structure is similar to atropine. • Arterial blood pressure: As with morphine. • There is a mild quinidine-like action that results in decreased myocardial excitability that in turn decreases the incidence of ventricular arrhythmias. This may be related to the local anesthetic-like action (membrane stabilizing action) of meperidine. • Unlike other opioids, large doses of meperidine decrease myocardial contractility. <p>5) Nausea and vomiting: As morphine.</p> <p>6) Histamine release:</p> <ul style="list-style-type: none"> • It is less than morphine. • It may have an anti-histaminic (H₁) action, so it can be used in bronchial asthma.

Fentanyl	Alfentanil	Sufentanil	Remifentanyl
<p>2) Central nervous effects:</p> <ul style="list-style-type: none"> • Sedation is less than morphine and meperidine. <p>3) Respiratory effects:</p> <p>It is similar to morphine except that:</p> <ul style="list-style-type: none"> • An intravenous bolus may produce a second delayed respiratory inhibition (up to 4 hours after i.v. bolus) due to its sequestration in gastric juice and subsequent absorption from the small intestine due to its high lipid solubility. • Chest wall muscle rigidity (stiff-chest syndrome): may occur due to a central mechanism. <p>It may affect respiratory compliance and hinder mechanical ventilation.</p> <p>It is prevented by non-depolarizing muscle relaxants and reversed by naloxone.</p> <p>4) Cardiovascular effects:</p> <ul style="list-style-type: none"> • Heart rate and arterial blood pressure are slightly decreased due to vagal stimulation. <p>5) Nausea and vomiting:</p> <p>It has a similar degree to that of other opioids.</p> <p>6) Histamine release:</p> <p>It is less than morphine or even absent.</p> <p>7) Smooth muscle:</p> <p>As morphine.</p>	<ul style="list-style-type: none"> • It decreases the heart rate and arterial blood pressure more than fentanyl especially in elderly and critically ill patients. • It interacts with erythromycin: after 7 day erythromycin course, alfentanil metabolism is impaired resulting in more sedation and respiratory depression. 		<p>2) Central nervous effects:</p> <ul style="list-style-type: none"> • It does not produce loss of consciousness. • There is no increase in ICP or convulsions. <p>3) Respiratory:</p> <ul style="list-style-type: none"> • It inhibits the respiratory center directly in a dose related manner. • Muscle rigidity occurs. <p>4) Cardiovascular effects:</p> <ul style="list-style-type: none"> • It is effective in blunting the pressor response to intubation • Mild bradycardia occurs.
<p>1) Intravenous route:</p> <ul style="list-style-type: none"> • For intraoperative analgesia: 1-2 µg/kg. • For major surgery (cardiac surgery): - Induction: 20-40 µg/kg i.v. slowly. - Maintenance: additional boluses of 5 µg/kg every 30-60 min or i.v. infusion of 0.3-1 µg/kg/min up to 50-150 µg/kg may be needed to produce an anesthetic state, but postoperative mechanical ventilation is essential. <p>2) Intravenous infusion.</p> <p>3) Oral transmucosal route.</p> <p>4) Inhaled/intranasal route.</p> <p>5) Patient controlled analgesia (PCA).</p> <p>6) Epidural PCA.</p> <p>7) Epidural route.</p> <p>8) Intrathecal route.</p> <p>For doses, advantages, and disadvantages of each, see chapter of pain management.</p>	<p>I.v. route:</p> <ul style="list-style-type: none"> • For intraoperative analgesia: 10-15 µg/kg • For major surgery (with mechanical ventilation planned): - loading 8-100 µg/kg then i.v. infusion of 0.5-3 µg/kg/min. 	<p>I.v. route:</p> <ul style="list-style-type: none"> • For intraoperative analgesia: 0.05 µg/kg • For major surgery as cardiac surgery (with mechanical ventilation planned): Induction: 5-30 µg/kg Maintenance: Either additional boluses of 1 µg/kg or i.v. infusion of 0.075 µg/kg/min. 	<p>I.v. infusion:</p> <ul style="list-style-type: none"> • Loading 1.0 µg/kg <p>Then followed by infusion of 0.5-2 µg/kg/min that may be increased up to 20 µg/kg/min.</p> <p>N.B.: It is presented as a lyophilized white crystalline powder containing glycine; therefore, it should not be used epidurally or intrathecally.</p>

Morphine	Meperidine (Pethidine)
<p>7) Effects on smooth muscles: a- Gastro-intestinal motility: <ul style="list-style-type: none"> • Peristaltic movement is suppressed resulting in: <ul style="list-style-type: none"> - delayed gastric emptying (hence vomiting may increase). - constipation on prolonged use due to <ul style="list-style-type: none"> • Decreased perception of sensory stimuli of defecation. • Increased tone of the sphincter and non-peristaltic movement. • Non-peristaltic movement is increased, resulting in: <ul style="list-style-type: none"> - Dehiscence of large bowel anastomosis. - Decreased absorption of oral drugs. <p>b- Sphincters: The tone of smooth muscles is increased resulting in spasm of the choledochoduodenal sphincter of Oddi (causing biliary colic), ureters, and urinary bladder sphincter (causing retention of urine). This is reversed by naloxone, glucagon, or nitroglycerin. It occurs in only < 3% of patients. Therefore, it is avoided in • Biliary or renal colic. <ul style="list-style-type: none"> • Premedication in cholecystectomy. • Prostatic hypertrophy. <p>N.B.: Biliary colic pain may be confused with angina pectoris; <ul style="list-style-type: none"> - Naloxone can relieve pain caused by biliary spasm, but it does not affect myocardial ischemia. - Nitroglycerin can relieve pain due to biliary spasm and myocardial ischemia. <p>c- Uterus: Prolonged and delayed labor may occur.</p> <p>8) Effects on pregnancy: <ul style="list-style-type: none"> • It prolongs labor. • It causes neonatal respiratory depression as it crosses the placenta during labor. • Neonates of chronic use mothers show withdrawal symptoms. <p>9) Effects on eyes: Miosis occurs due to stimulation of Edinger-Westphal nucleus of oculomotor nerve center.</p> <p>10) Endocrine effects: <ul style="list-style-type: none"> • All opioids are effective in suppressing the stress response to surgery, laryngoscopy, and intubation. This is measured by decreased release of catecholamines, anti-diuretic hormone, and cortisol. • They also decrease release of adreno-corticotrophin hormone (ACTH), follicular stimulating hormone (FSH) and leutinizing hormone (LH) resulting in infertility. <p>11) Hypothermia: Due to: • Reduced metabolic rate. • Vasodilatation. • Decreased muscle tone. • Impaired thermoregulation.</p> <p>12) Depression of the immune system: In long term use. Opioids depress immunological function and induce apoptosis of lymphocytes; therefore, there is increased incidence of viral infections as herpes after neuraxial opioids and increased infectivity described in HIV-positive patients receiving opioids.</p> <p>13) Pruritis: It is common in the nose and face especially after neuraxial block. It is reversed by naloxone.</p> </p></p></p></p></p>	<p>7) Effects on smooth muscles: a- Gastro-intestinal motility: It is reduced less than morphine. b- Sphincters: It relaxes the gastrointestinal and renal smooth muscles; therefore, it can be used in renal colic. c- Uterus: It does not prolong labor.</p> <p>8) Effects on pregnancy: <ul style="list-style-type: none"> • It does not prolong labor. • Neonatal respiratory depression may occur because it crosses the placenta, but it is less prolonged than morphine, so it is preferred in obstetrics. • Neonates of chronic use mothers show withdrawal symptoms. <p>9) Effects on eyes: Mydriasis occurs due to the atropine-like action.</p> <p>10) Drug interactions: a- All opioids especially meperidine interact with monoamino oxidase inhibitors (MAOIs), Levo-Dopa, or tyramine in food resulting in excitatory serotonergic syndrome (i.e., autonomic nervous system instability with hypertensive crisis, tachycardia, diaphoresis, hyperthermia, agitation, hyperreflexia, fits, and coma) then finally respiratory depression and death (it is one of the most fatal drug interactions). b- All opioids interact with other anesthetics such as N₂O, benzodiazepines, barbiturates, or volatile agents resulting in significant myocardial and respiratory depression and excessive sedation.</p> </p>
<p>It is taken by all routes as morphine sulfate or HCl.</p> <ol style="list-style-type: none"> 1) I.v. route: 0.1 mg/kg up to 1 mg/kg for intraoperative analgesia. 2) I.m. route: 0.2 mg/kg for postoperative analgesia. 3) I.v. infusion: 0.05-0.07 mg/kg/h. 4) Patient controlled analgesia (PCA). 5) Oral: sustained or immediate release tablets 0.4 mg/kg for chronic pain. 6) Epidural route: the same as i.v. dose. 7) Epidural PCA. 8) Intrathecal (spinal) route: 1/10 of i.v. dose. 9) Rectal. For doses, see chapter of pain management. 	<ol style="list-style-type: none"> 1) I.v. route: 0.5-5 mg/kg. 2) I.m. route: 1mg/kg. 3) I.v. infusion 0.1-0.3 mg/kg/h. 4) Epidural route: the same as i.v. dose. 5) Intrathecal (spinal) route: 1/10 of i.v. dose.

Opioid Antagonists

Mechanism of Action:

They bind to the opioid receptors, but produce **no effect**. They are **competitive antagonists**. Their affinity for μ receptors appears to be much greater than for kappa and delta receptors.

Naloxone (Narcan)

Chemical Structure:

It is related to oxy-morphine.

Onset: Within 1 min (after i.v. administration).

Duration: 20-30 min due to rapid redistribution from the brain.

Clinical Actions and Uses:

It antagonizes all the central nervous system effects of opioid agonists including analgesia as:

1- It antagonizes **opioid-induced ventilatory depression**:

- That occurs in **low doses**; therefore, the drug should be titrated slowly against the clinical effect to avoid antagonizing the analgesic effects.

- It is of a relatively **short duration**; therefore, it may cause returning of respiratory depression induced by longer-acting opioids. Patients should be monitored carefully for an appropriate period after its use as a further dose or i.v. infusion may be needed.

- It is of choice in **neonates** to reverse neonatal respiratory depression (asphyxia neonatorum) induced by opioids administered to the mother before delivery.

2- It antagonizes **opioid-induced coma or excessive sedation**:

Therefore, it is used in treatment of morphine or morphine-like drug toxicity.

3- It antagonizes opioid-induced **dependence**:

It helps in diagnosis of dependence produced by opioids as withdrawal symptoms appear after its administration.

4- It antagonizes **opioid-induced side effects of the epidural route**:

- For example, pruritis or urine retention.

5- It antagonizes **opioid-induced analgesia**:

- In **large doses**, it antagonizes analgesia; even analgesia of the spinal cord; causing pain that may stimulate the sympathetic system producing an **increase of heart rate, blood pressure, and arrhythmias including ventricular fibrillation**.

N.B.: • Naloxone is ineffective in ventilatory depression or sedation caused by;

- Buprenorphine due to the very high affinity of buprenorphine to μ receptors.
- Non-opioid drugs e.g., barbiturates or benzodiazepines.

- Naloxone may antagonize the antihypertensive effect of clonidine.

- Naloxone can be used to improve circulation in refractory shock.

Dose: (one ampoule = 0.2 or 0.4 mg/mL)

1- I.v. bolus: - Increments of 0.5-1 μ g/kg every 3-5 min (usually 0.2-0.4 mg in adult).

- Supplementary doses may be required after 20-30 min.

2- I.v. infusion: 4-5 μ g/kg/hr

3- I.m.: Twice the i.v. dose, with longer duration of action.

N.B.:

- Neonatal respiratory depression resulting from maternal opioid administration is treated with 10 μ g/kg.
- Neonates of opioid-dependent mothers will exhibit withdrawal symptoms if given naloxone.

Naltrexone (ReVia)

It is an analogue of naloxone, similar to naloxone in action, but with the following differences:

1- It only **antagonizes μ receptors**.

2- It is used as an adjunct to maintain an opioid-free state **after initial treatment of opioid-dependence** to prevent relapse.

3- It has a **longer** duration of action, up to **24 hours**.

4- It is given only **orally**.

Nalmefene (Revex)

It is an opioid antagonist with 11 hours duration of action.

It is given intravenously, intramuscularly, or subcutaneously.

BENZODIAZEPINES

Chemical Structure and Structure-Activity Relationship

- They contain a **benzene ring** and a **seven-member diazepine ring**, hence their name.
 - Midazolam contains an imidazole ring (it is an imidazobenzodiazepine) that increases its water solubility at a low pH (figure 3-19).
- Diazepam and lorazepam do not contain an imidazole ring; therefore, they are insoluble in water.

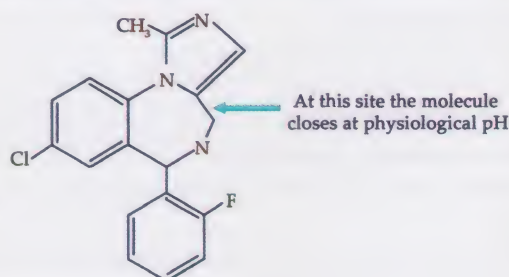


Figure 3-19: Midazolam

Mechanism of Action

- Benzodiazepines bind to the **γ -aminobutyric acid receptor type A (GABA_A receptor)** where they bind specifically to:
 - the **γ -subunit of GABA_A receptor producing anxiolysis and muscle relaxation**
 - and ▪ the **α -subunits of the same receptor producing sedation and anticonvulsant actions.**

These sites are called **benzodiazepine-recognition sites**. This binding increases affinity of the receptor to the GABA. The latter binds to the **β -subunit** of the GABA receptor which is called GABA recognition site. This action is mediated by an **increase in Cl⁻ entry into the cells**, resulting in **hyperpolarization** of the postsynaptic membrane, which in turn inhibits neuronal transmission (figure 3-20).

- The GABA_A receptor is a large structure which also contains separate binding sites for other drugs including barbiturates, alcohol, and propofol. This explains:
 - The **synergistic effects** seen with these drugs and benzodiazepines that may cause severe central nervous system depression.
 - The **cross-tolerance** seen with other drugs as alcohol.
 - The benefit of using benzodiazepines in **management of withdrawal symptoms or acute toxicity** from alcohol or other drugs.

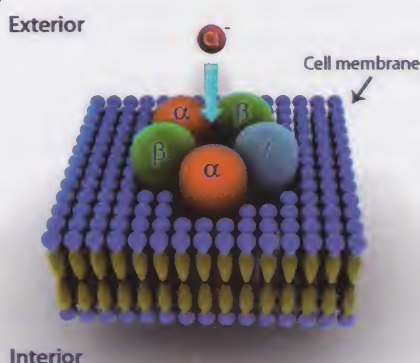


Figure 3-20: A GABA_A receptor

Types of GABA Receptors:

	GABA-A	GABA-B
Types	Ionotropic (acts directly via ion channels)	Metabotropic (acts via G proteins that act later on ion channels)
Ion channels	It increases Cl ⁻ channels	It increases K ⁺ efflux.
Other binding sites	Barbiturates and benzodiazepines	
Agonist	Muscimol	Baclofen
Antagonists	Bicuculline	Phaclofen
Site	Postsynaptic	Post- and presynaptic
Major role	Anti-nociceptive	Decreasing motor reflexes and allodynia.

Pharmacodynamics

1- Central Nervous Effects:

1- Sedative-hypnotic and anxiolytic action:

In a dose-related manner, benzodiazepines progressively produce anxiolysis, sedation, hypnosis and then finally anesthesia in large doses. Benzodiazepines have a high therapeutic index i.e., a high ratio of effective to lethal dose.

Therefore, they are used as:

- **sedative drugs** (especially midazolam) during
 - premedication before elective surgery.
 - regional anesthesia.
 - endoscopy and dental surgery.
 - cardioversion.
 - intensive care.
- **hypnotic drugs** in treatment of insomnia.
- **anxiolytic drugs** during
 - management of acute and chronic anxiety states.
 - management of acute alcohol withdrawal.
- **anesthetic drugs** for induction of anesthesia in cardiac surgery.

N.B.: The most common sedative drugs used in anesthesia and intensive care:

- Benzodiazepines.
- Neuroleptics.
- α_2 adrenoceptor agonists.
- Propofol at subanesthetic doses.
- Inhaled anesthetics at subanesthetic doses.
- Ketamine at subanesthetic doses.

2- Amnestic action:

Benzodiazepines produce dose-related **anterograde amnesia** (i.e., for events after administration) due to their effects on the early consolidation phase of memory processing. Lorazepam is the most efficient in producing amnesia.

Although it has been claimed that some benzodiazepines induce retrograde amnesia (i.e., for events before administration), this has never been demonstrated.

Therefore, they are used as a premedication.

3- Anticonvulsant action:

Through GABA facilitation, they prevent subcortical spread of the seizure activity (they do not affect the seizure focus activity itself).

Therefore, they are used as a broad-spectrum anticonvulsant drug especially in grand mal epilepsy.

4- **Tolerance (due to down regulation), physical and psychological dependence** may occur on chronic use, but it is less addictive than opioids.

Abrupt withdrawal causes symptoms similar to acute alcohol withdrawal; therefore, gradual decreasing of the dose is essential.

5- They **decrease cerebral metabolic rate of O_2 ($CMRO_2$), cerebral blood flow (CBF), and intracranial pressure (ICP)**, but less than barbiturates.

In contrast to propofol and thiopental, midazolam is unable to produce an isoelectric electroencephalogram (EEG), thus emphasizing that there is a ceiling effect on benzodiazepine-induced decrease in $CMRO_2$.

Midazolam does not also prevent the increase in ICP associated with intubation.

5- **Residual drowsiness and mental impairment** may persist for 24 hours **especially with diazepam**; therefore, patients should be instructed about the danger of driving or operating machinery or taking alcohol for the following 24 hours.

2- Respiratory Effects:

In large doses, **respiratory depression** may occur, resulting in short periods of apnea and reduced direct responses to hypoxia and hypercarbia especially in: - elderly or debilitated patients.

- patients on other respiratory depressants e.g., opioids.

They also may cross the placenta resulting in neonatal depression.

3- Cardiovascular Effects:

In large doses, **slight reduction of arterial blood pressure** (due to reduced systemic vascular resistance), and **cardiac output** are common.

Heart rate is slightly increased due to: - reflex tachycardia.
and - a vagolytic action.

This is more common: - with **midazolam** than with diazepam
- elderly and debilitated patients.
- hypovolemic and vasoconstricted patients.
- with opioids or other hypotensive agents.

4- Mild Relaxant Effects:

They produce mild relaxant effects, but inadequate for surgical access. This may cause airway obstruction on large doses.

This action is due to depression of polysynaptic transmission in the brain and spinal cord i.e., a central action; not due to an action on the neuromuscular junction.

Therefore, it is used in spastic states.

The Most Common Benzodiazepines Used in Anesthesia

	Diazepam (Valium)	Midazolam (Dormicum)	Lorazepam (Ativan)
Class	Long acting	Short acting	Medium acting
Pharmacokinetics	<ul style="list-style-type: none"> Solubility: It is relatively lipid soluble, so it has a relatively rapid onset; 30-45 min after oral route. 1-2 min after i.v. route. Rapid redistribution after i.v. intake which is responsible for awakening (as barbiturates) $t_{1/2\alpha} = 3-10$ min. Protein binding: is high 90-98% Metabolism: In the liver by microsomal oxidation (mainly) and conjugation with glucuronide, resulting in an active metabolite, which is called N-desmethyldiazepam. This metabolite accumulates in renal failure, resulting in prolongation of the action. Duration: Long 4-6 hours after oral route because: 1- Elimination half-life is prolonged 20-50 hours (average 36 hours). 2- High entero-hepatic circulation that results in a second peak of diazepam plasma concentration 6-12 hours after administration. 3- The active metabolite, N-desmethyldiazepam, has a long $t_{1/2\alpha}$ about 100 hours. Excretion: Via the kidney for water soluble metabolites. 	<ul style="list-style-type: none"> Solubility: It contains an imidazole ring that makes it water soluble at low acidic pH, as in its ampoule; but after injection, at the physiological pH of the body, the imidazole ring closes, which in turn increases its lipid solubility; therefore, rapid onset occurs. Onset: 90 seconds with i.v. route. Peak effect: 2-5 min with i.v. route. Redistribution: as diazepam. Protein binding: as diazepam. Metabolism: as diazepam, but no active metabolites are produced. Duration: It is short because: 1- Elimination half-life is short; 2 hours. 2- There are no active metabolites. N.B.: In some critically ill patients, the metabolism is reduced and the elimination $t_{1/2\alpha}$ may be prolonged up to 21 hours, resulting in delayed recovery of consciousness. Excretion: as diazepam. 	<ul style="list-style-type: none"> Solubility: It is moderately lipid soluble resulting in a slow onset. Redistribution: as diazepam. Protein binding: as diazepam. Metabolism: as diazepam but no active metabolites are produced. Duration: It is long, but less than diazepam because: 1- Elimination half-life is 15 hours. 2- It has a high affinity to receptors. 3- There are no active metabolites. Excretion: as diazepam.
Drug interactions	<ul style="list-style-type: none"> All benzodiazepines in low doses decrease the MAC of volatile anesthetics by 30%. All benzodiazepines potentiate the sedative effects of ethanol alcohol, barbiturates, and other central nervous system depressants. Cimetidine binds to cytochrome P-450, reducing the metabolism of diazepam. This increases the action of the latter. Heparin displaces diazepam from the plasma protein binding sites resulting in an increase in the free drug concentration which in turn increases the action. 		
		<ul style="list-style-type: none"> Erythromycin decreases the metabolism of diazepam; therefore, the action of the latter is prolonged. 	

Doses and preparations	<p><u>Presentations:</u> Diazepam is water insoluble; therefore, it is presented as:</p> <ul style="list-style-type: none"> • An emulsion in soya bean oil (Diazemuls). <p>or • A viscous solution containing organic solvents such as propylene glycol. This solvent produces thrombophlebitis in 50-60% of patients after i.v. administration. Therefore, Diazemuls is better.</p> <p>2 ml ampoule, 5mg/ml.</p> <p><u>Routes:</u></p> <ul style="list-style-type: none"> • Oral (tablets or syrup) given 1.5 hour before the induction. • I.v. bolus • Rectal. <p>- There is no i.m. route because it is painful and its absorption is slow, erratic and unpredictable.</p> <p>- There is no intravenous infusion because it has a very long half-life.</p> <p><u>Doses:</u></p> <ul style="list-style-type: none"> • For sedation and premedication: 0.1-0.2 mg/kg. • For status epilepticus: 2 mg. repeated every minute until the seizure ends, maximum dose is 20 mg. 	<p><u>Presentation:</u> 1 ml ampoule, 5 mg/ml 3 ml ampoule, 5mg/ml</p> <p><u>Routes and doses:</u></p> <ul style="list-style-type: none"> • I.m.: for premedication 0.05-0.15 mg/kg. • I.v.: <p>- For sedation and premedication: 0.01-0.1 mg/kg followed by i.v. infusion in intensive care of 0.03-0.1 mg/kg/h.</p> <p>- For induction of anesthesia: 0.1-0.4 mg/kg.</p> <ul style="list-style-type: none"> • Intranasal 0.2-0.3 mg/kg. • Buccal preparation: 0.07 mg/kg. • Sublingual: 0.1 mg/kg. <p>There is no oral route.</p>	<p><u>Routes and doses:</u></p> <ul style="list-style-type: none"> • Oral or i.m. routes: For premedication, 0.05 mg/kg given on the night of surgery. • I.v. bolus: For sedation, 0.03-0.04 mg/kg.
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Flumazenil

Chemical Structure:

It is an imidazobenzodiazepine.

Mechanism of Action:

It is a specific and competitive antagonist at benzodiazepine receptors. It occupies the receptor, but produces no activity. In very high doses, it has a slight agonist effect.

Onset: < 1 min.

Duration: 20 min -2 hours.

Metabolism:

It occurs in the liver. The elimination half-life is < 1 hour.

In liver diseases, the duration of benzodiazepines and flumazenil is prolonged.

Pharmacodynamics:

It reverses all central effects of benzodiazepines especially sedation, amnesia, hypnosis, and respiratory depression; therefore, it can be used in patients with overdosage of benzodiazepines, or even to diagnose patients with sedation and/or respiratory depression of unknown origin.

Side Effects:

1- It has a **relatively short duration**; therefore, **sedation and respiratory depression may return**, so patients should be monitored carefully for an appropriate period and repeated doses or infusion may be needed. **Elderly patients** appear to be difficult to fully reverse and are **more prone** to re-sedation.

2- It may induce **seizures in epileptic patients** if benzodiazepines are used in their treatment.

3- It may **precipitate withdrawal symptoms** in patients on prolonged treatment of benzodiazepines.

4- It **increases ICP** in patients with head trauma.

5- Nausea and vomiting may occur.

Doses: (5 ml ampoule, 0.1 mg/ml)

Ex. route: 0.1-0.2 mg increments at 1-min intervals until reaching the desired degree of reversal (usually 0.6-1.0 mg).

Repeated doses within 1-2 hours or intravenous infusion of 0.1-1 mg/h may be needed.

NEUROLEPTICS

(Anti-psychotic, Major Tranquilizers, or Ataractics)

Many of these drugs are used in anesthesia and intensive care as premedication drugs, sedatives, antiemetics, and in neurolept-analgesia/anesthesia. They include:

A) Butyrophenones: as Haloperidol (*Haldol*)

Droperidol.

B) Phenothiazines: as Chlorpromazine (*Thorazine*).

Perphenazine (*Trilafon*)

Fluphenazine (*Prolixin*)

Trifluoperazine (*Stelazine*)

Thioridazine (*Mellaril*)

C) Thioxanthines: Thiothixene (*Navane*)

D) Atypical Drugs: Risperidone (*Risperdal*)

Clozapine (*Clozanil*)

Quetiapine (*Seroquel*)

Olanzapine (*Zyprexa*)

Ziprasidone (*Geodon*)

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Mechanism of Action:

1- They **block dopamine receptors** (dopamine is a stimulatory neurotransmitter); this explains their neuroleptic, antiemetic and the extrapyramidal effects. Atypical antipsychotic drugs block subtypes of dopamine receptors (especially D₂ and D₃) and subtypes of serotonin receptors (especially 5-HT_{2A}); therefore, they produce less side effects.

2- They **enhance GABA receptors** (GABA is an inhibitory neurotransmitter); this explains their sedative effects.

3- They **block also cholinergic, α- adrenergic, histaminergic, and serotonergic actions.**

Pharmacokinetics

90% is metabolized in the **liver** to soluble end products that are excreted by the kidney.

10% is excreted unchanged in the urine and bile.

Pharmacodynamics

1- Central Nervous Actions:

1- Neuroleptosis (Antipsychotic Action):

It is a drug-induced state, which occurs due to block of dopamine receptors (D₂). There are:

- Suppressed spontaneous movements.
- Lack of initiative, disinterest in the environment and a placid appearance.
- Little display of emotions.

But with:

- No loss of consciousness.

- No amnesia.
- Unpleasant sensations.
- Intact spinal and central reflexes.
- Intact intellectual functions.

Uses: In treatment of psychosis e.g. schizophrenia or organic psychosis.

Neurolept-Analgesia:

• It is **neuroleptosis** with **analgesia** without loss of consciousness.

It is induced by a neuroleptic agent as droperidol and a potent analgesic agent as fentanyl.

- Uses: as **sedatives** if they are used in moderate doses, as in:
 - Minor surgical procedures.
 - Regional anesthesia e.g. ophthalmic surgery.

They were famous before the advent of i.v. benzodiazepines.

• In large doses, profound respiratory depression without loss of consciousness occurs i.e., the patient becomes hypoxic and cyanotic, but remains conscious and responds to orders to breathe, as **Ondine's curse**.

Neurolept-Anesthesia:

• It is **neurolept-analgesia** (in large doses) with N₂O (that causes loss of consciousness).

It is similar to the dissociative anesthesia of ketamine.

- Uses: Induction of anesthesia in - cardiac surgeries.
and - neurosurgeries.

2- Sedative Action:

They have a weak intrinsic sedative action, but they potentiate sedative and anesthetic drugs and may cause delayed recovery of anesthesia.

3- Antiemetic Action:

It is due to blocking of the dopamine receptors in chemoreceptor trigger zone.

They are effective in: • drug (e.g., opioids) and disease-induced vomiting.

- postoperative vomiting.

They are ineffective against motion sickness

4- They **decrease cerebral blood flow and intracranial pressure** due to their cerebral vasoconstrictive action, but they do not decrease cerebral metabolic rate of O_2 ($CMRO_2$), unlike barbiturates, benzodiazepines and etomidate.

5- **Abnormal Motor Effects:** (due to blocking of the dopamine receptors)

They include: • **Extrapyramidal manifestations** as mask-like facies, a festinating gait, and cogwheel rigidity. They are common in children and elderly.

- **Akathisia or akathisia:** it is an irresistible urge to move (inability to sit still) (extreme restlessness).

- **Acute dystonia:** it is skeletal muscle spasm in the tongue, face, neck (torticollis), and mouth and oculogyric crisis.

- **Tardive dyskinesia:** (involuntary choreoathetoid movements of the tongue, lip smacking, truncal instability).

- **Rabbit syndrome:** it is periorbital tremors.

Therefore, they are **contraindicated in a patient with Parkinsonism**.

Neuroleptic Malignant Syndrome:

It is a rare fatal complication of **neuroleptic drugs** especially **phenothiazines and butyrophenones** as **haloperidol**, which occurs hours or weeks after administration of neuroleptic drugs (such as butyrophenones and phenothiazines), due to **central postsynaptic dopamine blockade** in the basal ganglia and hypothalamus.

Other causative drugs:

- Antiemetic agents as metoclopramide, droperidol, and prochlorperazine.
- Central nervous stimulants as amphetamine and cocaine.
- **Discontinuation of dopaminergic drugs** as amantadine, bromocriptine, and levodopa

Clinical Picture:

There is **muscle rigidity, hyperthermia, rhabdomyolysis**, tachycardia, autonomic dysfunction and instability, altered consciousness, acidosis, and increased creatine kinase.

The mortality rate is 30% due to renal failure or arrhythmias.

It is very **similar to malignant hyperthermia**, but in neuroleptic malignant syndrome:

- A normal muscle biopsy is present.
- Inhalational anesthesia and succinylcholine are not contraindicated.

Treatment: • Supportive measures.

- Dopamine agonist e.g., bromocriptine.
- Dantrolene therapy.

6- Hypothermic Action:

They block the effects of thermogenic amines such as catecholamines, serotonin, and acetyl choline. They also decrease postoperative shivering. Their alpha-blocking action produces peripheral vasodilatation which helps in producing hypothermia.

7- Endocrine Action:

They **stimulate release of prolactin**; therefore, galactorrhea, gynecomastia, and amenorrhea may occur.

2- Respiratory Action:

In the usual low doses, a **little effect on respiration** occurs. In large doses, respiratory depression may occur especially if other respiratory depressant drugs are used concomitantly as opioids.

6- Cardiovascular Action:**1- Arterial Blood Pressure:**

- Hypotension (**orthostatic hypotension**) occurs especially in hypovolemic patients and after a large i.v. dose.

- It does not occur with haloperidol.

- This is due to:

- blocking of the peripheral postsynaptic α_1 -adrenergic receptors, resulting in vasodilatation.
- blocking of the central presynaptic α_2 -adrenergic receptors, resulting in decreased sympathetic outflow.

2- Heart Rate:

Reflex tachycardia due to baroreceptor reflex and the atropine-like action.

3- Arrhythmias:

• **Droperidol** causes a **prolonged QT syndrome and Torsades de pointes**; therefore, electro-cardiography (ECG) should be done before its administration. If QT is prolonged, it should not be given; and even if QT is normal, droperidol is given with **ECG monitoring** for the following 2-3 hours.

• **Droperidol** should be **avoided in pheochromocytoma** because it increases the release of catecholamines from the adrenal medulla resulting in arrhythmias and hypertension.

4- Autonomic Actions:

Beside the α -adrenergic blocking action, **they have an anti-cholinergic (atropine-like) action** that may cause dry mouth, constipation, tachycardia, and urinary retention.

Drug Interactions:

Neuroleptics **potentiate central nervous depressants** as sedatives, anesthetics, or opioids.

Neuroleptics **antagonize** - dopaminergic agonists as dopamine.

- Levo-dopa resulting in increasing Parkinsonian syndrome.
- ketamine resulting in decreasing its cardiovascular actions.
- Clonidine resulting in rebound hypertension.

Individual Drugs:**Droperidol**

Onset: 3-10 min after i.v. administration.

Duration: > 12 hours due to its high affinity to the receptors.

Routes: oral, i.m., and i.v. bolus.

Dose: • For premedication and antiemetic action: 0.04-0.07 mg/kg.

• For neurolept-analgesia/anesthesia: up to 10 mg + fentanyl \pm N₂O.

Thalamonal or Innovar: it is a mixture of droperidol 2.5 mg/ml + fentanyl 50 μ g/ml.

Haloperidol (*Haloperidol, Haloprol, Haldol decanoas, or Saffinace*)

It is similar to droperidol except: • it has a more delayed onset; 5-20 min after i.v. or i.m. administration.

- it has a more prolonged duration up to 12-24 hours.
- there is no α -adrenergic blocking action.
- these are more extra-pyramidal side effects.
- dose: 6-20 mg/day orally
2-5 mg i.v. or i.m.

Chlorpromazine (*Largactil, Neurazine, or Promacid*)

It is taken by the oral, i.v. and i.m routes: 25-50 mg, 1 hour before anesthesia.

SKELETAL MUSCLE RELAXANTS

Physiology of Neuromuscular Junction

Release of Acetylcholine:

- When an **impulse (an action potential)** reaches the terminal of the motor neuron, **Ca⁺⁺ influx** occurs via voltage-gated calcium channels, resulting in fusion of the storage vesicles containing acetylcholine (ACh) with the neuron membrane and **releasing the ACh**. ACh is synthesized from choline and acetyl coenzyme "A" by the enzyme choline acetyltransferase.
- ACh diffuses across the synaptic cleft, a gap 20-60 nm between the cell membranes of the neuron and muscle fiber, and **binds with the nicotinic cholinergic receptor**. There is a very large safety margin of both the amount of ACh released and the receptors. There are about 5 millions receptors in the neuromuscular junction, but activation of only about 0.5 million receptors is needed for muscle contraction (figure 3-21). Only 20% of the released ACh reaches the postsynaptic nicotinic receptors where the remaining 80% are destroyed by the neuronal acetylcholinesterase enzyme.

N.B.: Botulinum toxin interferes with the fusion of the ACh vesicles to the cell membrane and prevents release of ACh resulting in paralysis.

Nicotinic Receptors:

There are two types of nicotinic receptors according to their location:

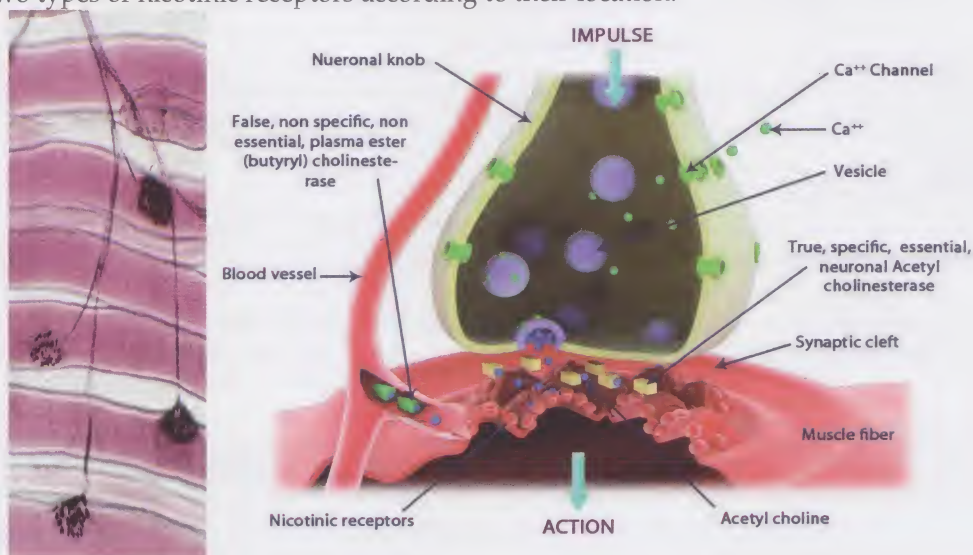


Figure 3-21: The neuromuscular junction

a- Prejunctional (presynaptic) nicotinic receptors: they are found presynaptically on the motor nerve terminal. These receptors are activated by ACh and function in a positive feedback control system that maintains availability of ACh when demand for it is high. Blocking of these receptors by nondepolarizing muscle relaxants decreases the mobilization of ACh which **causes the fade phenomenon**.

The presynaptic nicotinic receptor is structurally distinct from the postsynaptic ACh receptor. It is composed of 5 subunits; **three alpha (α) and two beta (β)**.

b- Postjunctional (postsynaptic) nicotinic receptors: they are present at a specialized portion of the muscle membrane which is called the **motor end-plate**. It consists of 5 subunits; **2 alpha (α), one beta (β), one delta (δ), and one epsilon (ε)**. In the fetus, or in extra-junctional receptors, the receptors are immature where a **gamma (γ) subunit** replaces the epsilon (ε) subunit (figure 3-22). These five units are arranged as a cylinder around a central, normally closed, channel called "**ionophore**".

Binding:

- ACh contains one **quaternary ammonium group with positively charged nitrogen** that **binds** only to the **α-subunit** to produce the action. **The two α-subunits must** be occupied simultaneously by ACh to produce opening of the ion channels in the core of the receptor for only a very short period about 1 ms. If only one α-subunit is bound to ACh, the ion channels will not open and the action potential will not occur.

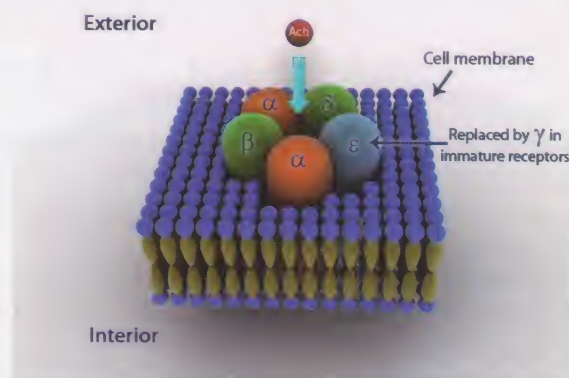


Figure 3-22: The nicotinic receptor

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- Stimulation of nicotinic receptors will **open ion channels** (Na^+ and Ca^{++} in while K^+ out according to their concentration gradients), generating an **end-plate action potential** where the membrane potential of the muscle cell is changed from the -80 mV resting state to +40 mV active state.
- When an adequate number of end-plate potentials accumulate, adjacent voltage-gated Na^+ channels in the muscle membrane are opened and a muscle action potential, which activates muscle contraction, is started.

Contraction of the Muscle:

- The resulting action potential propagates along the muscle with release of Ca^{++} from the sarcoplasmic reticulum. The intracellular Ca^{++} allows the contractile protein actin and myosin to interact, resulting in muscle contraction.

Relaxation of the Muscle:

- ACh in the synaptic cleft and that binds to the receptor is **rapidly hydrolyzed** into acetate and choline (that is reused in re-synthesis of ACh) by the **true, substrate-specific, essential, neuronal cholinesterase** enzyme.
- Then the nicotinic receptors become free from ACh and their ion channels close, causing the end-plate to repolarize and calcium is re-sequestered back in the sarcoplasmic reticulum and the muscle fiber relaxes.

N.B.: The amine groups present in some drugs are either:

Tertiary Amines	Quaternary Amine
<ul style="list-style-type: none"> • They make drugs more lipid-soluble. • The drugs can cross easily physiological membranes such as cell membranes, blood brain barriers, and placenta, and are excreted in the milk. • The drugs have a more rapid onset and a shorter duration. • The drugs can be given by any route whether orally, intravenously, intramuscularly, as eye drops...etc. • Examples: - All local anesthetics. - Atropine. - Physostigmine. 	<ul style="list-style-type: none"> • They make drugs more water-soluble as they contain highly positive charges. • The drugs can not cross easily. • The drugs have a more delayed onset and a more prolonged duration. • The drugs can be given only by i.v. route. • Examples: - All muscle relaxants. - Glycopyrrolate - Neostigmine.

Mechanism of Action of Muscle Relaxants

Depolarizing (non-Competitive) Relaxants	Non-depolarizing (Competitive) Relaxants
<p>1. Phase I Block (Depolarizing):</p> <ul style="list-style-type: none"> • They resemble acetylcholine (ACh) in structure; therefore, they bind to ACh receptors and produce muscle action potential i.e., ACh receptor agonists. • Unlike ACh, they are not metabolized by the true acetylcholinesterase; therefore, they react repeatedly with receptors as one will be attached to the receptor after the other is separated. These repeated actions produce prolonged depolarization of muscle end- 	<ul style="list-style-type: none"> • They bind to one or two of α subunits in ACh nicotinic receptors (as they have at least one quaternary ammonium group $\text{N}^+(\text{CH}_3)_3$ that binds to α-subunits), but they are incapable of inducing the conformational changes necessary for ion channel opening i.e., the channel remains closed. ACh is prevented from binding to its receptor and no end-plate potentials occur i.e., competitive inhibition. There is no fasciculation. N.B.; This explains: • Conditions with a chronic decrease in ACh release (e.g.,

plates which in turn **opens sodium channels**. The sodium channels **then close** (as it is time-limited); once the channel closes, disappearance of muscle action potential occurs and **muscle relaxation** follows. These sodium channels, after the initial excitation, opening and closure, cannot reopen until the end-plate repolarizes which is not possible as long as the depolarizing muscle relaxant continues to bind to ACh receptors.

- In other words, there is **fasciculation** followed by flaccid relaxation.

2 Phase II Block (Desensitization, 2ry non-Depolarizing, Dual Block):

- It occurs on **repeated** or **prolonged** administration of **suxamethonium** which produces a block clinically resembling a non-depolarizing block.

- This is **due to receptor desensitization i.e., ionic and conformational changes** that occur in the receptors due to prolonged muscle membrane depolarization.

- It is treated by an anticholinesterase e.g., **neostigmine**.

muscle denervation injuries) stimulate a compensatory increase in the number of immature extra-junctional ACh receptors i.e., **up regulation**. This causes an exaggerated response to depolarizing muscle relaxants (with more receptors being depolarized), but a resistance to non-depolarizing muscle relaxants (more receptors that must be blocked).

- Conditions with decreased ACh receptor numbers (e.g., myasthenia gravis) i.e., **down regulation** or decreased release of ACh (e.g., Eaton-Lambert myasthenic syndrome) cause resistance to depolarizing muscle relaxants and increased sensitivity to non-depolarizing muscle relaxants.

- **Fade**: is due to the pre-junctional effect of non-depolarizing muscle relaxants that decreases the amount of ACh in the nerve terminal available for release during stimulation i.e., blockade of ACh mobilization.

- **Posttetanic potentiation**: is due to a compensatory increase in the presynaptic ACh and in Ca^{++} mobilization as a result of the positive feedback effect of the tetanic stimulation. ACh cannot be released due to the rapid tetanic stimulation, and instead, it accumulates in the presynaptic terminals and on a subsequent twitch, release occurs in large amounts, resulting in potentiation.

Reversal of the Block:

- No specific agent is used to reverse depolarizing blockade, but the depolarizing muscle relaxants (which are not metabolized by true acetylcholine esterase) are hydrolyzed in the plasma and the liver by **pseudo-cholinesterase (non-specific, plasma, false, non-essential) enzyme** and their concentration falls in the plasma. After that, the depolarizing muscle relaxants diffuse away from the neuromuscular junction to the plasma according to the concentration gradient, leaving the receptor free to be occupied later by the natural transmitter ACh.

- An anticholinesterase (e.g., **neostigmine**) produces:
 - inhibition of acetylcholinesterase, resulting in an increase in the ACh at the neuromuscular junction, so the block intensifies.
 - inhibition of pseudo-cholinesterase, resulting in a decrease in the hydrolysis of suxamethonium, so the block also intensifies.

Reversal of the Block:

- With the exception of mivacurium, non-depolarizing muscle relaxants are not significantly metabolized by either acetylcholinesterase or pseudo-cholinesterase. Reversal of their blockade depends on **redistribution away from the neuromuscular junction, gradual metabolism and excretion**.

- An anticholinesterase (e.g., **neostigmine**) produces: **inhibition of acetylcholinesterase**, resulting in an increase in ACh amounts available at the neuromuscular junction that compete with the non-depolarizing muscle relaxants. This produces reversal of the block.

Response to Peripheral Nerve Stimulators:

Response to Peripheral Nerve Stimulators	Depolarizing Blockade		Non-Depolarizing Blockade
	Phase I	Phase II	
Train of four	Decreased but constant	Fade	Fade
Tetany	Decreased but constant	Fade	Fade
Double burst stimulation	Decreased but constant	Fade	Fade
Posttetanic potentiation	Absent	Present	Present

More details are discussed in the chapter of "Basic Physics for Anesthesia & Intensive Care".

The Muscle Relaxant Effect of Other Drugs

- **Inhalational anesthetic agents, local anesthetics and ketamine** produce muscle relaxation by **interfering with the normal functioning of the ACh receptor-binding sites**.

- **Neostigmine, some antibiotics as streptomycin or gentamycin, cocaine, and some antiarrhythmics as quinidine or lidocaine** produce muscle relaxation by acting on the ion channels (ionophores); either during their closure or opening.

a- During closed channel blockade: the drugs physically plug up the channel, preventing passage of cations whether ACh binds to the receptor or not.

b- During open channel blockade: the drugs enter inside the channels and obstruct them only when the channels are opened by ACh binding.

Therefore, increasing the concentration of ACh with anticholinesterases does not overcome the muscle blockade.

Depolarizing Muscle Relaxants

Suxamethonium chloride (Succinylcholine or Diacetylcholine)

Chemical Structure:

It is a **quatery ammonium** compound (amine). It consists of two acetylcholine molecules linked together (figure 3-23). The two radicals N^+ $(CH_3)_3$ have the capacity to bind to each of the α -subunits of postsynaptic ACh receptors.

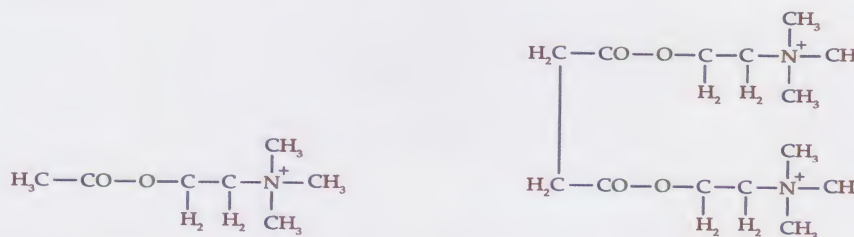


Figure 3-23: Acetylcholine (left) and succinylcholine (right)

Storage:

It should be stored in a refrigerator (**2-8 °C**) and should generally be used within 14 days after removal from the refrigerator due to its chemical hydrolysis.

Dose:

- 1.0 - 1.5 mg/kg i.v.
- **Uncommonly, repeated small boluses (10 mg)** or a **succinylcholine infusion** (1 g in 500 or 1000 ml, titrated to effect) are used during some surgical procedures that require brief, but intense paralysis (e.g., in laryngoscopic procedures) with the following precautions:
 - Methylene blue indicator dye is often added to succinylcholine drips to prevent confusion with other i.v. fluids.
 - Neuromuscular function should be constantly monitored with a nerve stimulator to prevent overdosing and the development of phase II block.
- 4-5 mg/kg i.m.

In infants and neonates, due to a larger extracellular space than adults, the suxamethonium (water soluble) is distributed in this larger extracellular space and requires greater dosage than adults.

Onset:

30-60 sec (to reach 95% block). It is the **most rapid** of all muscle relaxants. (N.B.: the onset of rocuronium almost equals that of succinylcholine).

Duration:

Recovery starts within 3 min and is complete within 12-15 min (25% recovery at 10 min).

Indications:

Its usage is decreased nowadays and some clinicians restrict its usage only to tracheal intubation in the following conditions:

- Patient with full stomach or undergoing obstetric surgery.
- Difficult tracheal intubation is expected (to reach the optimum conditions for intubation).

Pharmacokinetics:

Metabolism:

- In plasma by - **pseudo-cholinesterase** (98-99%) at a very rapid rate, producing succinylmonocholine.
 - other nonspecific esterases.
- In the liver (very minimal).

Excretion:

- By the kidneys either as - water soluble inactive metabolites (mainly), or
 - unchanged in urine (10%).

Causes of Prolongation of Duration of Action (Succinylcholine Apnea):

i.e., abnormal metabolism.

a. Inherited Factors:

Plasma cholinesterase structure is determined genetically by autosomal genes where the normal typical homozygous enzyme is ($E_1^u E_1^u$). Gene abnormalities cause abnormal structure.

1- **Dibucaine-resistant gene or atypical gene (E_1^a)** (in 4% of Caucasians).

- Heterozygote (E_1^a , E_1^a): prolonged action of suxamethonium, about 20-30 min.
- Homozygote (E_1^a , E_1^a): prolonged action of suxamethonium up to 4-8 hours.

2- **Fluoride-resistant gene or fluoride gene (E_1^F)**: rare.

3- **Silent gene (E_1^S)**:

- Homozygote (E_1^S , E_1^S): prolonged action of suxamethonium > 3 hours up to 24 hours.

It has a very small capacity to metabolize suxamethonium; therefore, the latter is actually metabolized by nonspecific esterases in plasma.

Treatment:

1- Keep the patient **anesthetized (to avoid risk of awareness)** and **artificially ventilated** (to avoid hypoxia).

2- **Monitor neuromuscular transmission** accurately until full recovery from residual neuromuscular blockade occurs.

3- **Fresh frozen plasma** or fresh blood may be administered as they contain cholinesterase enzyme.

4- **Studying the details of the genetic status** of the patient and the immediate relatives. A plasma sample is taken to **measure the patient's cholinesterase activity**; it should be taken **several days after the prolonged block** has been discovered because suxamethonium decreases plasma cholinesterase level in the plasma.

Detection of the abnormal cholinesterase structure is done by the following method:

- If the plasma of a normal genotype patient is added to a water bath containing a substrate as **benzylcholine**, a chemical reaction occurs with plasma cholinesterase as benzylcholine reacts with the normal enzyme. This reaction will emit **light of a given wavelength** which can be detected by a **spectrophotometer**.

- Addition of **dibucaine** (a local anesthetic) to the water bath inhibits pseudo-cholinesterase and inhibits this reaction; therefore, no light is produced.

- Dibucaine inhibits **normal pseudo-cholinesterase** activity by ~ 80 %,
- but it inhibits the **heterozygous** enzyme by ~ 40- 60 %
- and inhibits the **homozygous** enzyme by ~ 20 %

The percentage of inhibition of pseudo-cholinesterase activity is called **dibucaine number** which is proportional to the pseudo-cholinesterase function and independent of the amount of the enzyme (figure 3-24).



Figure 3-24: Detection of abnormal cholinesterase structure

- Addition of fluoride to the water bath (instead of dibucaine) allows detection of fluoride gene. Fluoride causes inhibition of the reaction. It typically parallels dibucaine inhibition.

- If light does not occur after mixing of patient's plasma and benzylecholine, this indicates the silent gene.

5- A **warning card or an alarm bracelet** is given to patients after discharge from the hospital.

Acquired Factors:

The activity of plasma cholinesterase is decreased, although the structure is normal, causing prolonged action of suxamethonium for a few minutes.

Causes:

1- Decreased enzyme synthesis as in: liver diseases, starvation, carcinomatosis, and pregnancy.

2- Decreased enzyme activity as in: hypothyroidism and hypothermia.

3- Increased enzyme removal as in: plasmapheresis and cardiopulmonary bypass.

4- Renal disease.

5- Anti-cholinesterases inhibit both acetylcholinesterase and pseudo-cholinesterase.

6- Other drugs that are metabolized by plasma cholinesterase decrease its availability as:

- Etomidate
- Ester local anesthetics
- Mivacurium
- Metoclopramide.
- Oral contraceptives.
- Esmolol.
- Monoamino oxidase inhibitors as phenelzine.
- Anticancer drugs as methotrexate and cyclophosphamide.

N.B.: Pancuronium decreases the enzyme activity, but is not metabolized by the enzyme.

Side Effects:

1- **Succinylcholine apnea:** see above.

2- **Postoperative muscle pain (postoperative myalgia):**

- It is most probably due to initial fasciculations.
- Common in: patients who are ambulant soon after surgery as day-case patients.
patients who have a large muscle mass as young fit patients.
female patients.
- Rare in extremes of age and pregnancy (as usually the fasciculations are absent).
- Site of pain: in unusual sites as the diaphragm and between the scapulae.
- Treatment: pain is not relieved by conventional analgesics.
- Prevention:

1. Precurarization (pretreatment):

A small dose (10-15%) of nondepolarizing muscle relaxant is given immediately (5 min) before suxamethonium e.g., gallamine 10 mg (which is the most efficacious), atracurium 2.5 mg, or rocuronium 0.1 mg/kg. This will decrease the potency of suxamethonium; therefore, larger doses of suxamethonium, about 1.5 mg/kg, should be used to get the same effect (as already some receptors will be occupied by the small amount of nondepolarizing muscle relaxant).

2. Other drugs have been tried but none of them are completely reliable: such as lignocaine, Ca^{++} , Mg or repeated doses of thiopentone.

3- **Cardiovascular effects:**

• At the usual low doses, suxamethonium and its metabolite succinylmonocholine stimulate muscarinic receptors in the SA node leading to a direct vagal effect, and in cardiac muscle leading to decreased contractility i.e., **negative inotropic and chronotropic actions**.

This is common in: ▫ Patients with high vagal tone as children and physically fit individuals.

▫ Repeated doses of suxamethonium within 3-8 min after the first dose.

Therefore, it is advisable to give anticholinergics routinely especially in these conditions.

• At higher doses, the heart rate and contractility usually increase i.e., **positive chronotropic and inotropic actions**, because suxamethonium stimulates nicotinic receptors in sympathetic ganglia and adrenal medulla and also elevates the catecholamine level.

4- **Hyperkalemia:**

• Normally, muscles release about 0.5 mmol/L K^+ during suxamethonium administration, and that may be due to muscle fasciculation. This is insignificant in normal persons with normal K^+ levels, but in patients with preexisting hyperkalemia, resistant cardiac arrest may occur.

• The hyperkalemia produced is not affected (i.e., no benefit) by precurarization.

• Conditions associated with hyperkalemia include:

1. **Denervation injuries** in muscles, that cause proliferation of extra-junctional immature receptors (i.e., up regulation), for example,

- Poly-neuropathies.
- Severe Parkinson's disease.
- Paraplegia.
- Spinal cord injury.
- Guillain-Barré syndrome.
- Tetanus.
- Myopathies as muscular dystrophies or dystrophia myotonica.

Suxamethonium is considered **contraindicated** in the routine management of **children and adolescents** due to the risk of rhabdomyolysis, hyperkalemia, and cardiac arrest in those with undiagnosed myopathies.

2. **Massive tissue trauma**, for example,

- Poly-trauma.
- Closed head injury, encephalitis and stroke.
- Severe intra-abdominal infections.
- Hemorrhagic shock with metabolic acidosis.
- Burn injury.

They cause tissue destruction which results in increased s. K^+ .

The risk of hyperkalemia usually appears **from the 4th day up to the 10th week** after injury (with a peak effect at 7-10 days), but the exact time of onset and duration of the risk is variable.

3. **Renal failure;** as already serum K^+ is high.

5- Malignant hyperthermia:

- Suxamethonium is a potent triggering agent. It increases the chance from 1: 250 000 with other anesthetic drugs up to 1: 60 000 with suxamethonium (i.e., nearly **5-folds**).
- Suxamethonium may cause contraction of the masseter muscles resulting in **difficult intubation**. This may be a warning sign of malignant hyperthermia.

6- Increased intra-gastric pressure:

- In the presence of a normal lower esophageal sphincter, the increased intragastric pressure by abdominal muscle fasciculation is not sufficient to produce regurgitation because the increased intragastric pressure is offset by an increase in the lower esophageal sphincter tone.
- In patients with incompetent esophageal sphincter e.g., hiatus hernia, regurgitation may occur.
- **Precurarization abolishes** the rise of both gastric pressure and lower esophageal sphincter tone.

7- Increased intraocular pressure:

- It is due to fasciculation of the external ocular muscles.
- It is **not abolished by precurarization**.
- It lasts as long as the neuro-muscular block lasts.
- It may cause expulsion in open eye injury.

8- Increased intracranial pressure:

- Suxamethonium slightly increases cerebral blood flow, intracranial pressure, and cerebral activity with activation of electroencephalogram.
- Increased cerebral activity occurs because muscle fasciculations stimulate muscle stretch receptors which subsequently increase cerebral activation.
- This can be **abolished by precurarization**.

9- Anaphylactic reactions: they are rare. On repeated exposure, histamine release may occur.**Decamethonium**

It is an old depolarizing agent not used nowadays.

It has a rapid onset as suxamethonium, but a longer duration (20 min),

It is not metabolized by plasma cholinesterase but mainly excreted unchanged via the kidney.

Q: What are the different doses of muscle relaxants?

A: There are many doses:

1. Intubating dose: to facilitate the insertion of the endotracheal tube. It is 2-3 times the effective dose 95% (ED₉₅). ED₉₅ is the effective dose of a drug in 95% of individuals.
2. Loading (initial) dose: is used after insertion of the tube by a depolarizing agent. It is usually ½ the intubating dose.
3. Maintenance (incremental) dose: it is given repeatedly intraoperatively every certain time according to the duration of the agent used; it is better adjusted by a nerve stimulator.
4. Infusion dose: is used mainly with short or intermediate agents during long surgeries or in intensive care units.
5. Precurarization dose: is discussed before.
6. Priming dose: is discussed below.
7. Intramuscular dose: with some agents and in certain circumstances when the i.v. access is not available.

Nondepolarizing Muscle Relaxants

They include:

A- Benzylisoquinolinium Compounds:

- | | | |
|-------------------------------|---------------------------|--------------------------------------|
| 1- d-tubocurarine (obsolete). | 2- Metocurine (obsolete). | 3- Alcuronium (obsolete). |
| 4- Gallamine (rarely used). | 5- Atracurium. | 6- Cis-atracurium (the most recent). |
| 7- Mivacurium. | 8- Doxacurium. | |

They tend to release histamine.

B- Aminosteroid Compounds:

- | | | |
|-----------------|--|----------------|
| 1- Pancuronium. | 2- Pipecuronium | 3- Vecuronium. |
| 4- Rocuronium. | 5- Rapacurium (withdrawn from the market). | |

They tend to be vagolytic.

N.B.: Due to structural similarities between the two groups, an allergic history to one muscle relaxant highly suggests the possibility of allergic reactions to other muscle relaxants.

A- Benzyliisoquinolinium Compounds:

	Atracurium Besylate (<i>Tracrium</i>)	Cis-atracurium (<i>Nimbex</i>)	Mivacurium	Doxacurium
Chemical structure: There is at least one quaternary amine that binds to the α -subunit of nicotinic receptors	<ul style="list-style-type: none"> • Mono-quaternary amine • It must be stored at 2-8 °C in a refrigerator as it loses 5-10% of its potency every month if it is exposed to room temperature. It should be used within 14 days if it is left at room temperature. 	<ul style="list-style-type: none"> • It is the R-Cis -R' Cis isomer of atracurium. • It must be stored as atracurium. It should be used within 21 days if it is left at room temperature. 	<ul style="list-style-type: none"> • Bis-quaternary amine. • It is stored at room temperature 	<ul style="list-style-type: none"> • Bis-quaternary amine
Onset To reach 95% block	Moderate (2-3 min)	Moderate (2-3 min)	Moderate (2-3 min)	Slow (4-6 min)
Duration (After intubating doses)	Intermediate acting (20-30 min)	Intermediate acting (45-60 min)	Short acting (10-20 min)	Long acting (120-150 min)
Dose - Loading = $\frac{1}{2}$ of intubating dose. - Incremental = $\frac{1}{4}$ of the loading dose or $\frac{1}{10}$ of the intubating dose.	<ul style="list-style-type: none"> • Intubating: 0.5 mg/kg • Loading: 0.25 mg/kg • Incremental: 0.1 mg/kg every 20 min • Infusion 5-10 μg/kg/min. 	<ul style="list-style-type: none"> • Intubating 0.1 mg/kg (4-5 times more potent than atracurium) • Infusion 1.0 - 2.0 μg/kg/min. 	<ul style="list-style-type: none"> • Intubating: 0.15 mg/kg. • Loading: 0.08 mg/kg • Incremental: 0.05 mg/kg. • Infusion: 5-10 μg/kg/min. 	<ul style="list-style-type: none"> • Intubating: 0.05 mg/kg (the most potent) • Loading: 0.02 mg/kg • Incremental 0.005 mg/kg every 20-40 min
Metabolism & Excretion	<ul style="list-style-type: none"> • Hoffmann degradation: 45% i.e., spontaneous non- enzymatic breakdown at physiologic temperature and pH that changes it from quaternary to tertiary amine called laudanosine, so it is safe in patients with renal or liver dysfunction. Laudanosine is epileptogenic (may not be so in humans even with large doses?). • Ester hydrolysis in plasma by nonspecific esterases: 40% (not by true or false cholinesterases). • Kidney or bile excretion: 10%. 	<ul style="list-style-type: none"> • Hoffmann degradation: mainly. Because it is more potent than atracurium, fewer doses are required; therefore, less laudanosine is produced. • No effect for nonspecific esterases. 	<ul style="list-style-type: none"> • Plasma cholinesterase (95-99%). It may not need anticholinesterase for reversal (if neuromuscular function is monitored). If plasma cholinesterase abnormality is inherited or acquired, the duration of action is increased e.g., renal or hepatic failure (although not eliminated by them). In contrast to suxamethonium, its block is reversed by anticholinesterase. • Kidney: < 5% • True cholinesterase: Minimal %. 	<ul style="list-style-type: none"> • Kidney: (mainly) > 90% • Plasma cholinesterase 6%
Side Effects • Allergic reaction may occur with all of them • To decrease the side effects, slow administration of muscle relaxant (over 1-3 min) is essential.	<ol style="list-style-type: none"> 1. Histamine release: (+) less ($\frac{1}{3}$ of tubocurarine) with atracurium, resulting in less symptoms; but no histamine release occurs with cis-atracurium. 2. Cardiovascular system: no direct effects. 3. Laudanosine toxicity: It stimulates the central nervous system resulting in increased MAC, and may cause fits (but not in humans). This occurs with high doses or with hepatic failure (as it is metabolized in the liver). 4. Hypothermia or acidosis decreases Hoffmann degradation, resulting in increased duration of action. 5. They precipitate as a free acid if mixed in a venous line containing an alkaline solution as thiopentone.➤ 		1 and 2 as atracurium	1 and 2 as cis-atracurium.

B- Aminosteroid compounds:

Pancuronium Bromide (<i>Pavulon</i>)	Pipecuronium (<i>Arduan</i>)	Vecuronium (<i>Norcuron</i>)	Rocuronium (<i>Esmeron</i>)
<ul style="list-style-type: none"> • Bis-quaternary amine • It must be stored at 2-8°C but it is stable for 6 months at room temperature. 	<ul style="list-style-type: none"> • Bis-quaternary amine • It is a pancuronium analogue. 	<ul style="list-style-type: none"> • Mono-quaternary amine • It is a pancuronium analogue. 	<ul style="list-style-type: none"> • Mono-quaternary amine • It is a vecuronium analogue.
Moderate (2-3 min)	Moderate (2-3 min)	Moderate (2-3 min)	Rapid 60-90 sec with the high dose , so it is suitable for rapid sequence induction.
Long acting (60-90 min)	Long acting (60-90 min)	Intermediate (45-60 min)	Intermediate (30-40 min)
<ul style="list-style-type: none"> • Intubating: 0.08-0.1 mg/kg • Loading: 0.04 mg/kg • Incremental: 0.01 mg/kg Every 30-45 min. 	<ul style="list-style-type: none"> • Intubating: 0.08-0.1 mg/kg 	<ul style="list-style-type: none"> • Intubating: 0.08-0.1 mg/kg • Loading: 0.04 mg/kg • Incremental 0.01 mg/kg every 15-20 min • Infusion 1-2 µg/kg/min 	<ul style="list-style-type: none"> • Intubating: 0.3-0.6 mg/kg • Incremental: 0.1 mg/kg. • Infusion 5-10 µg/kg/min (as atracurium) • I.m. 1-2 mg/kg with 3-6 min onset.
<ul style="list-style-type: none"> • Kidney: 60% • Liver: 30%. Active metabolites are produced which are excreted by the kidney. • Bile excretion: 10% 	<ul style="list-style-type: none"> • Kidney: 60% • Liver: 20% • Bile: 20% 	<ul style="list-style-type: none"> • Kidney: 40% • Liver: 5% • Bile: (mainly) 70% An active metabolite is produced; 3-hydroxy vecuronium that accumulates during long term infusion in the intensive care N.B.: The dose should be decreased in biliary obstruction and in liver diseases (as they are associated with biliary stasis). 	<ul style="list-style-type: none"> • Kidney: 40% • Liver: insignificant • Bile: (mainly) 60%. No active metabolites are produced; therefore, it is more suitable for prolonged intensive care infusion than vecuronium.
<ol style="list-style-type: none"> 1. Histamine release: No 2. Cardiovascular system: Potent vagolytic effect and some direct sympatho-mimetic (+) increasing blood pressure and heart rate 3. It inhibits plasma choline esterase; potentiating drugs metabolized by this enzyme e.g., suxamethonium and mivacurium. 	1 and 2 as Cis-atracurium	<ol style="list-style-type: none"> 1 and 2 as cis-atracurium. 3. It precipitates with thiopental, resulting in thrombo-embolism of the i.v. line that may cause pulmonary embolism. 4- Avoided in long term infusion in the intensive care (see below). 	1 and 2 as pancuronium

The Most Recent Muscle Relaxant:**Gantacurium**

Chemical structure: it is a new benzyloquinolinium nondepolarizing muscle relaxant. It has a single isomer, unlike mivacurium or atracurium where there are many isomers.

Onset: It is faster than mivacurium, and needs 60-70 seconds to reach 100% block.

Duration: It is ultra-short and shorter than mivacurium; 10 minutes to reach ED₉₅ and 12-15 minutes to reach 4 x ED₉₅.

Dose: It has a similar potency to mivacurium; ED₉₅ = 0.19 mg/kg
2-3 x ED₉₅ = 0.38-0.54 mg/kg

Side effects: It causes histamine release with transient hypotension and tachycardia at high doses.

It is reversed by edrophonium 0.5 mg/kg.

Metabolism: There are two chemical non-enzymatic mechanisms:

a- Rapid hydrolysis: addition of cysteine, a nonessential amino acid, to the gantacurium compound at the site of the chlorine molecule results in rapid hydrolysis of the ganatcurium with production of mixed-onium thiazolidine as a major metabolite.

b- Slow hydrolysis: slow hydrolysis of the ester bond occurs adjacent to the chlorine substitution giving inactive metabolites.

N.B.: Addition of cysteine (10 mg/kg) i.v. 2 minutes after the administration of 8 x ED₉₅ gantacurium shortens the 5% to 95% recovery interval by 2.5 minutes and the total duration of the block (to ≥ 0.9 train-of-four ratio) by 6.5 minutes. Cysteine (10 mg/kg) will facilitate complete recovery of the neuromuscular function even when administered within 1 minute of gantacurium.

Other muscle relaxants not used now:

a- Benzyloquinolinium Compounds:

	d-Tubocurarine	Metocurine	Alcuronium	Gallamine (Flexidil)
Chemical structure There is at least one quaternary amine that binds to the α -subunit of nicotinic receptors	<ul style="list-style-type: none"> • Mono-quaternary amine. • It is the only natural muscle relaxant. 	<ul style="list-style-type: none"> • Bis-quaternary amine • It is a derivative of tubo-curarine (di-methyl tubo-curarine) 		<ul style="list-style-type: none"> • Tri-quaternary amine It is rarely used nowadays.
Onset To reach 95% block	Moderate (2-3 min)	Moderate (2-3 min)	Moderate (2-3 min)	Moderate (2-3 min)
Duration (after the intubating dose)	Long acting (100-120 min)	Long acting (100-120 min)	Long acting (100-120 min)	
Dose	<ul style="list-style-type: none"> • Intubating: 0.5-0.6 mg/kg • Loading: 0.15 mg/kg • Incremental: 0.05 mg/kg every 30 min. 	<ul style="list-style-type: none"> • Intubating: 0.3 mg/kg • Loading: 0.08 mg/kg • Incremental 0.03 mg/kg every 30 min 	<ul style="list-style-type: none"> • Intubating: 0.2 mg/kg 	<ul style="list-style-type: none"> • Intubating: 160 mg in adults.
Metabolism & Excretion	<ul style="list-style-type: none"> • Kidney: (mainly) 60-80% • Bile: 10% • Liver: insignificant 	<ul style="list-style-type: none"> • kidney: (mainly) 98% • Bile: < 5% • Liver: insignificant 	<ul style="list-style-type: none"> • kidney: (almost entirely) 100% 	<ul style="list-style-type: none"> • kidney: (almost entirely) 100%
Side Effects • Allergic reaction may occur with all of them	1. Histamine release: (++) causes hypotension, reflex tachycardia, bronchospasm, and skin flare. 2. Cardiovascular system (CVS): Ganglion blockade in large doses which potentiates the previous C.V.S. effects. 3- It triggers malignant hyperthermia .	1. Histamine release: (+) less (1/2 of tubocurarine), causes less CVS effects, less bronchospasm, and less skin flare. 2. CVS: ganglion blockade less (than tubocurarine)	1. Histamine release: (+) causes less CVS effects, less broncho-spasm, and less skin flare. 2. CVS: Some vagolytic effect causes mild increases in heart rate. 3- It triggers malignant hyperthermia .	1. Histamine release: No 2. CVS: Potent vagolytic effect and some direct sympathomimetic (+) increasing blood pressure and heart rate 3. It crosses placenta , so not used in obstetrics.

b- Aminosteroid Compounds:

Rapacuronium

It is a vecuronium analogue. It has the most rapid onset, within 60 seconds, and has a short duration of action, 10-20 minutes. It is mainly excreted by the kidneys with insignificant liver elimination. It produces slight histamine release but has been **withdrawn from the market** because it produces **severe bronchospasm**.

Important Notes

• **Long-term administration of vecuronium**, either through repeated injections or infusion, to **patients in intensive care units** has resulted in prolonged neuromuscular blockade (**up to several days**).

Due to: - Accumulation of its active metabolite 3-hydroxy vecuronium.

- Changing drug clearance.
- Development of polyneuropathies.
- Prolonged lack of ACh binding at the postsynaptic nicotinic ACh receptors. This mimics a chronic denervation state and causes lasting receptor dysfunction and paralysis.

Risk factors: - Female gender.

- Renal failure.
- Long-term or high-dose corticosteroid therapy.
- Sepsis.

• Some clinicians administer the muscle relaxant e.g., rocuronium just before the administration of the induction agent such as propofol to compensate its slightly prolonged onset (**the timing principle**), but there is a possibility of delayed administration of the induction agent e.g., accidental removal of the i.v. line or presence of i.v. line precipitates, resulting in a conscious but paralyzed patient.

• The drug is usually administered incrementally every $\frac{1}{2}$ the duration of the intubating dose e.g., if the clinical duration of the intubating dose is 30 min, the drug is given in incremental doses every 15 min.

Q: Give accounts on a muscle relaxant e.g. rocuronium?

A: Discuss:

1. Chemical structure.
2. Mechanism of action.
3. Onset and duration.
4. Dose.
5. Metabolism and excretion.
6. Indications.
7. Side effects.
8. Reverse.
9. Monitoring and the type of block.
10. Drug interactions.
11. Factors affecting onset and duration.

Q: What are the non-relaxant effects of muscle relaxants?

A: Discuss the side effects of depolarizing and non-depolarizing muscle relaxants.

N.B.: Differences between Fasciculation and Fibrillation

The motor unit is a group of muscle fibers supplied by one nerve fiber ending.

The muscle fibers are about: 15 for a delicate movement muscle e.g., of finger.

> 100 for a crude movement muscle e.g., of back.

Fasciculations	Fibrillations
<ul style="list-style-type: none"> • Are contractions of separate motor units abnormally occurring out of phase with each other i.e., asynchronous motor unit contractions. • They indicate a neuronal cause because the muscle fibers within each unit respond synchronously. 	<ul style="list-style-type: none"> • Are contraction of separate muscle fibers abnormally occurring out of phase with each other i.e., asynchronous muscle fiber contractions. • They indicate a neuromuscular junction or muscle fiber cause.

Factors Affecting the Onset of Nondepolarizing Muscle Relaxants:

To speed the onset of nondepolarizing muscle relaxants:

1. Increase the Dose:

This increases the side effects e.g., 0.15 mg/kg of pancuronium produces relaxation in 90 sec, but increases hypertension and tachycardia and prolongs the blockade up to 60 min.

2. Give a Priming Dose:

Method: give 10-15% of the usual intubating dose 5 minutes before induction.

Value: it speeds the onset for intubation e.g., 60 sec for rocuronium

90 sec for other intermediate-acting relaxants.

Mechanism: this small priming dose will occupy enough receptors so that paralysis will quickly follow when the balance of the relaxant is given.

It does not usually cause clinically significant paralysis because that requires 75-80% of receptors to be blocked (a neuromuscular margin of safety).

Side Effects: in some patients, the priming dose occupies enough receptors to produce:

- Dyspnea or dysphagia.
- Muscle weakness.
- Significant reduction in the respiratory function that may produce hypoxia.

Therefore, if this occurs, induction of anesthesia should proceed without delay.

Q: What are the factors affecting muscle relaxants action?

A: Discuss factors affecting suxamethonium duration and the factors affecting the onset and the duration of the nondepolarizing muscle relaxants.

Factors Affecting Duration of Nondepolarizing Muscle Relaxants:

1. Body Temperature:

Hypothermia potentiates blockade by either:

- decreasing the metabolism e.g., atracurium and mivacurium
- or - decreasing the excretion e.g., tubocurarine, metocurine, and pancuronium.

For example: during cardiopulmonary bypass the dose of muscle relaxants should be decreased.

2. pH Changes:

Metabolic (and to a lesser extent respiratory) **acidosis potentiates** blockade with mono-quaternary amines.

3. Electrolyte Changes:

- Hypokalemia potentiates blockade.
- Hypocalcemia potentiates blockade by decreasing presynaptic ACh release.
- Hypercalcemia produces an unpredictable response.
- Hypermagnesemia potentiates blockade by competing with Ca^{++} at the motor end-plate as in pre-eclampsia.

4. Age:

- **Neonates** show **increased block** due to increased sensitivity of the immature neuromuscular junction to nondepolarizing muscle relaxants, but this does not necessitate decreasing the dosage because the neonate's greater extracellular space provides a larger volume of distribution which may cause **resistance** to the usual dosage.
- Children of **school age** show some **resistance** to the usual doses.
- **Elderly** patients show an **increased block** due to deterioration of organs which decrease metabolism and excretion.

5. Concurrent Diseases:

- **Hepatic failure and chronic renal failure** change pharmacokinetics of drugs as they increase the volume of distribution that, in turn, decreases plasma concentration for a given dose of water soluble agents as muscle relaxants, but drugs dependent on hepatic or renal excretion show prolonged elimination.

Therefore, the net effect is usually: a **greater loading** dose and a **smaller incremental** dose.

- In **myasthenia gravis**, there is a decrease in the number and half-life of postsynaptic receptors by autoantibodies produced by the thymus gland, so patients are **more sensitive** to the effect of nondepolarizing muscle relaxants but may show **resistance to suxamethonium**.

6. Muscle Groups:

The onset and intensity of blockade vary among muscle groups. This is due to the differences in:

- their blood flow,
- their distance from the central circulation,
- and • in the agent used.

In general, the **diaphragm, jaw, laryngeal muscles and orbicularis oculi** respond to and recover from muscle relaxation **earlier** than the thumb.

7. Drug Interactions of Muscle Relaxants:

1. Nondepolarizing muscle relaxants + suxamethonium:

- Non-depolarizing muscle relaxants **antagonize suxamethonium in phase I block** (as non-depolarizing muscle relaxants occupy some ACh receptors, so depolarization by suxamethonium is partially prevented as occurs in precurarization). An exception to this interaction is **pancuronium** as it **augments suxamethonium** blockade by inhibiting pseudo-cholinesterase.
- Nondepolarizing muscle relaxants **potentiate suxamethonium in phase II block**.
- Similarly, an intubating dose of **suxamethonium potentiates** the blockade of **nondepolarizing muscle relaxants**.

2. Others:

a- Drugs **potentiating both** depolarizing and nondepolarizing muscle relaxants:

- Antibiotics (streptomycin, polymixin, tetracycline, **gentamycin**, and clindamycin).
 - Antiarrhythmics (quinidine, **lidocaine**, **Ca^{++} channel blockers**, and procainamide).
 - Antihypertensive drugs (**trimethaphan** and **nitroglycerin** affect **pancuronium** only).
 - **Inhalational** agents; desflurane > sevoflurane > isoflurane and enflurane > halothane > N_2O .
- Generally, they decrease the doses of muscle relaxants by about 15%.
- **Local anesthetics.**

- **Mg sulfate.**
- ↳ Drugs **potentiating** nondepolarizing muscle relaxants only:
 - Ketamine.
 - Dantrolene.
- ↳ Drugs **potentiating depolarizing and inhibiting nondepolarizing** muscle relaxants:
 - Anticholinesterases (e.g., neostigmine), see above for the mechanisms.
- ↳ **Furosemide** has a biphasic effect.
 - Less than 10 µg/kg —→ it **potentiates both**.
 - From 1 to 4 mg/kg —→ it **inhibits both**.
- Q: What are the abnormal responses to skeletal muscle relaxants?
- A: Discuss for both depolarizing and nondepolarizing relaxants
 - Causes of prolonged duration of action.
 - Causes of antagonism of action.
 - Abnormal unexpected actions as malignant hyperthermia.

Reversal of Nondepolarizing Muscle Relaxants

- A reversal agent (an anticholinesterase) should be routinely given to patients who have received nondepolarizing muscle relaxants unless:
 - full reversal can be demonstrated (e.g., sustained tetany 100-Hz for 5 sec), or
 - the postoperative plan includes continued intubation and ventilation (adequate sedation must be provided).

For the mechanism of action of anticholinesterase (see before).

- Prior or concomitant administration of an anticholinergic agent as atropine sulfate (0.02 mg/kg) or glycopyrrolate (0.01 mg/kg) is essential to antagonize the muscarinic effects of the anticholinesterase.

Factors Affecting Reversal:

1- The Degree of Neuromuscular Blockade:

The dose of anticholinesterase depends on the degree of the neuromuscular blockade:

- More intense blocks require a greater dosage of the reversal agent. No amount of anticholinesterase can immediately reverse a severe blockade (with no response to tetany of a peripheral nerve stimulator). Excessive doses of anticholinesterase may prolong the block.
- It is safer to have some degree of spontaneous recovery i.e., the first twitch of the train of four before anticholinesterases are given, because their effectiveness depends on the degree of recovery present when they are given.

2- The Choice and Dose of Anticholinesterases:

- Edrophonium reversal is usually faster than neostigmine.
- Larger doses of neostigmine produce faster reversal than small doses, but there is no extra benefit in administering neostigmine at more than 75 µg/kg.

3- The Type of the Muscle Relaxant being Antagonized:

- Short- and intermediate-acting muscle relaxants are easily reversed and require a lower dose of reversal agent (for the same degree of blockade) than long-acting muscle relaxants.
- Mivacurium, a very short agent, may not need an anticholinesterase for its reversal.

4- Presence of Diseases:

For example: a patient with renal failure in whom pancuronium has been used, or with liver diseases in whom vecuronium has been used, a deeper block is produced which is difficult to be reversed.

Cholinesterase Inhibitors (Anticholinesterases)

They include:

- Simple alcohol: Edrophonium (with quaternary ammonium group).
- Carbamic acid esters (carbamates): - Neostigmine and pyridostigmine (quaternary amines).
- Physostigmine (tertiary amine).
- Organophosphorus compounds.

Pharmacological Action:

They activate the following receptors:

1- Muscarinic Receptors:

Stimulation of muscarinic receptors produces muscarinic action (parasympathetic actions) such as:

- **Cardiovascular system:** negative chronotropic (heart rate), inotropic (contractility), and dromotropic (conduction) actions.
- **Respiratory system:** bronchospasm and increased secretion (rhinorrhea and bronchorrhea). Respiratory failure is the main cause of death due to the above causes in addition to skeletal muscle paralysis and inhibition of the respiratory center.
- **Gastrointestinal tract:** increased peristalsis, salivation, and sphincter relaxation; resulting in nausea, vomiting, and diarrhea.
- **Exocrine glands:** profuse secretions such as tearing, rhinorrhea, bronchorrhea, and salivation
- **Eye:** miosis.

Therefore, anticholinesterase administration is important.

b- Nicotinic Receptors of Skeletal Muscles:

- They reverse nondepolarizing muscle relaxants (as above).
- They produce muscle relaxation and paralysis in large doses.

c- Central receptors:

Only the organophosphorus compounds and physostigmine (tertiary amine) can cross the blood brain barrier resulting in diffuse central nervous system activation; both nicotinic and muscarinic actions. This leads to **cognitive dysfunction, generalized convulsions, coma and respiratory arrest.**

Individual Anticholinesterases:

	Edrophonium	Neostigmine (Prostigmine, Epistigmine, or Amostigmine)	Pyridostigmine (Mestinon or Pystinon)	Physostigmine
Chemical structure	<ul style="list-style-type: none"> • Simple alcohol. • Quaternary amine (water soluble) 	<ul style="list-style-type: none"> • Carbamates. • Quaternary amine (water soluble) 	<ul style="list-style-type: none"> • Carbamates. • Quaternary amine (neostigmine analogue) 	<ul style="list-style-type: none"> • Carbamates. • Tertiary amine (lipid soluble).
Mechanism All of them inhibit cholinesterase enzymes; both the true and the false	<ul style="list-style-type: none"> • It produces reversible inhibition where it binds to the enzyme by electrostatic and hydrogen bonds (i.e., ionic non-covalent bond). It is a short lived weak bond (2-10 min). 	<ul style="list-style-type: none"> • They produce reversible inhibition where they bind to the enzyme by ester covalent bond. It is a medium-lived bond (3-4 hours). 		
Clearance	50-75% by the kidneys. 25-50% by the liver. Any increase in the duration of action of nondepolarizing muscle relaxants due to renal or hepatic impairment is accompanied by an increase in the duration of action of cholinesterase inhibitors.			It is almost completely metabolized by plasma esterases.
Onset	• 1-2 min (the most rapid).	• 2 min, initial effect. • 5-7 min, maximum effect	• 10-15 min	
Duration	• Few minutes (the shortest).	• > 1 hour	• > 2 hours (3-4 hours)	• 15-30 min
Doses	0.5-1 mg/kg	• 0.04-0.08 mg/kg i.v. In practice, many clinicians use a dose of 0.04 mg/kg (half-dose) if the preexisting blockade is mild to moderate, and a dose of 0.08 mg/kg (full-dose) if the blockade is intense. • 15 mg/6 hours orally.	• 0.1-0.4 mg/kg (it is 4 times more potent than neostigmine).	• 0.01-0.03 mg/kg
The recommended anticholinergic agent (both atropine and glycopyrrolate can be used)	• Atropine 0.015-0.02 mg/kg	• Glycopyrrolate 0.01 mg/kg. • In pregnancy, atropine is a better choice as neostigmine may rarely cross the placenta and cause fetal bradycardia, so atropine can antagonize this muscarinic effect in the fetus as it also crosses the placenta.	• Glycopyrrolate	• An anticholinesterase is usually not needed, but if it is given, atropine is chosen because glycopyrrolate does not cross the blood brain barrier and does not reverse the central effects of physostigmine.

Uses	<ul style="list-style-type: none"> • Reversal of nondepolarizing muscle relaxant: it is not effective to reverse long acting agents or profound muscle relaxation because the blockade may outlast the effect of Edrophonium where re-blockade may occur after an initial period recovery. • A diagnostic test for myasthenia gravis, and to differentiate between myasthenia gravis and cholinergic crisis. 	<ul style="list-style-type: none"> • Reversal of nondepolarizing muscle relaxants. • Myasthenia gravis. • Urinary bladder atony. • Paralytic ileus. • Intrathecal neostigmine (50-100 µg) is used as adjuvant to prolong sensory and motor blockade by inhibiting the breakdown of spinal cord acetylcholine. 	<ul style="list-style-type: none"> • Myasthenia gravis. 	<ul style="list-style-type: none"> • Central anticholinergic syndrome (toxicity): caused by overdosage of atropine or scopolamine as they cross the blood brain barrier. • Reverse brain depression caused by morphine, benzodiazepines, antidepressants, or volatile agents. • Eye glaucoma. • Alzheimer's disease where ACh is decreased in the brain. • Preventing postoperative shivering.
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Choice of Anticholinergic Agents:

• **Atropine** is a tertiary amine, so it is lipid soluble, with a rapid onset and short duration, and can cross the blood brain barrier.

Therefore, it is more suitable to be used with: - edrophonium (rapid onset and short duration although it is a quaternary amine).
- physostigmine (tertiary amine).
- neostigmine in a pregnant female.

Both the atropine and these anticholinesterases will have a rapid onset and a short duration; in other words, they start to act together and last nearly for the same duration.

• **Glycopyrrolate** is a quaternary amine, so it is water soluble, with a delayed onset and prolonged duration.

Therefore, it is more suitable to be used with: - neostigmine (quaternary amine).
- pyridostigmine (quaternary amine).

Both the glycopyrrolate and these anticholinesterases will have a delayed onset and prolonged duration; in other words, they start to act together and last nearly for the same duration.

Organophosphorus Compounds (Organophosphates)

They include:

a- Nerve Agents:

- Sarin.
- Soman.
- Tabun.

They are used as chemical warfare agents.

b- Insecticides:

- Di-isopropyl fluorophosphate (DFP).
- Tetra-ethyl pyrophosphate (TEPP).

They are used as pesticides (insecticides).

Both nerve agents and insecticides are tertiary amines, so they are absorbed readily via the lungs and skin among farm workers and soldiers. Insecticides are oily, less volatile liquids with a slower onset to toxicity with longer-lasting effects, while nerve agents are typically watery and volatile, acting rapidly and severely, but for a shorter period of time.

c- Eye Medications:

- Echothiophate.

It is used in treatment of narrow angle glaucoma as it produces miosis. It is a quaternary amine.

Mechanism of Action:

They produce **irreversible inhibition** of the cholinesterase enzyme as they produce **phosphorylation** of the enzyme by a very stable covalent long-lived bond. The phosphorylated enzyme complex undergoes a process of aging i.e., further strengthening of the covalent bond. Recovery occurs only on generation of a more new enzyme which takes some weeks.

Clinical Picture of Toxicity:

Excessive muscarinic, nicotinic, and central nervous effects, as above, that finally end by coma and death.

Treatment:

1- **Prophylactic pyridostigmine** is used in those threatened by chemical warfare with these compounds.

2- **Symptomatic and supportive treatment:** as

- aspiration of bronchial secretions.
- artificial ventilation.
- anticonvulsants as diazepam.

3- **Decontamination** to prevent further absorption such as removal of contaminated clothes, washing of skin, and gastric lavage.

4- **Atropine:** to antagonize the muscarinic and central nervous effects. 1-2 mg every 5-15 min until signs of adequate atropinization such as dry mouth and increased heart rate > 70 beat/min occur. Patients should be kept fully atropinized for at least 24 hours.

5- **Cholinesterase re-activators (oximes):**

Some oxime molecules combine to the unoccupied sites of the cholinesterase enzyme while other molecules attract the phosphorous atom from the enzyme (as they have high affinity to the phosphorous atoms and remove the organophosphorous compound from the enzyme) leading to activation of the enzyme especially if the complex has not been aged; therefore, oximes should be given within the first 12 hours of poisoning before aging occurs. Oximes also split organophosphorous into rapidly metabolizable fragments. Oximes include:

- **Paralidoxime (PAM):** 1-2 g (15-30 mg/kg) i.v. or i.m. It acts on the neuromuscular junction.
- **Diacetylmonoxime (DAM) or obidoxime:** they can cross the blood brain barrier.

All these agents are prepared as auto-injectors.

Sugammadex

It is a new reversal agent for non-depolarizing muscle relaxants by a new different mechanism.

Chemical Structure:

Cyclodextrins are chemical compounds, which are sugar derivatives.

Sugammadex is γ -cyclodextrin, a large molecule sugar derivative, and consists of 8 oligosaccharides arranged in a cylindrical structure to encapsulate all four steroid rings of a muscle relaxant as rocuronium completely.

Mechanism of Action:

- It encapsulates or chelates nondepolarizing neuromuscular relaxants in plasma, preventing their access to the nicotinic receptors and encouraging their dissociation from them.
- Sugammadex has a hydrophobic exterior and a hydrophilic internal cavity which can form an inclusion complex with hydrophobic substrates. The cavity of γ -cyclodextrin is large enough to fit steroidal muscle relaxants (figure 3-25). The bound muscle relaxant cannot be released any more and becomes inactive.
- The complex is then excreted in the urine and has no muscarinic or central nervous effects.

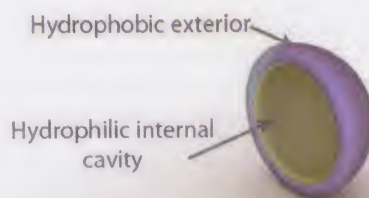


Figure 3-25: Sugammadex

Uses:

It is mainly used to chelate rocuronium and vecuronium with less action with pancuronium (aminosteroid compounds). It is drug specific, as sugammadex cannot antagonize atracurium. It has been approved and is used now in Europe.

LOCAL ANESTHETICS

Theories of Local Anesthetic Actions:

Sodium channel is composed of **one large α -subunit**, through which sodium ions pass and **one or 2 smaller β -subunits**. Most local anesthetics bind to the α -subunit and block voltage-gated sodium channels from inside the cells. Inactivation of sodium channels prevents its opening and subsequently no Na^+ influx occurs and so no membrane depolarization or action potential follow. Inactivation of sodium channels may occur by one of the following ways:

1- **Local anesthetics are Na^+ channel blockers**: most of local anesthetics **bind to Na^+ channels** (simply plug them from inside).

• On preparation, local anesthetics are usually prepared in an acid solution as HCl salt (pH 6-7). Epinephrine-containing local anesthetics are prepared in more acidic solutions (pH 4-5) as epinephrine is unstable in alkaline media. In acidic preparations, the **tertiary amine** group of the local anesthetic becomes **quaternary** making it more water soluble and suitable for injection and dilution with normal saline (figure 3-26).

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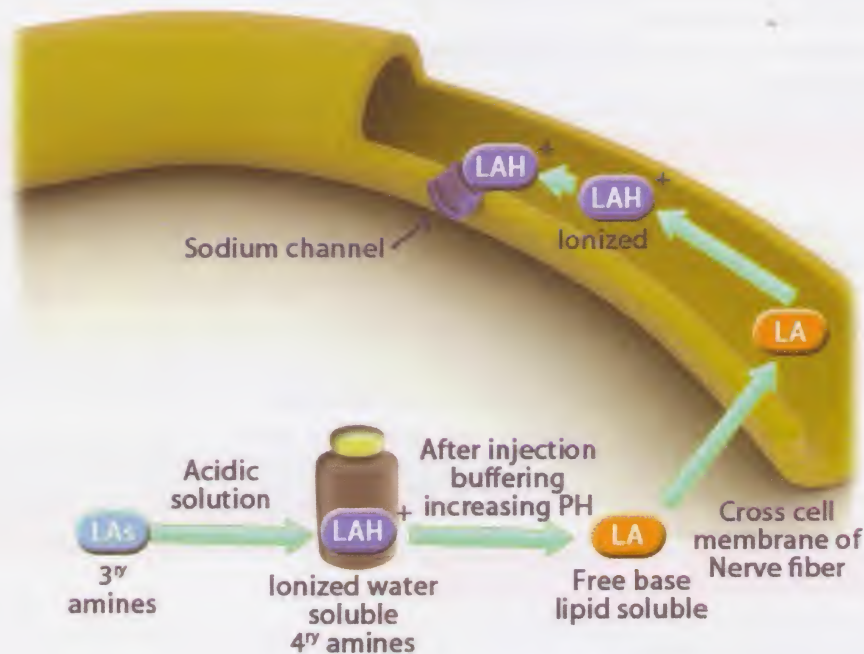


Figure 3-26: Mechanism of action of local anesthetics

• After injection in the tissues, the pH increases due to buffering in the tissues; therefore, a proportion of the drug, determined by pKa, **dissociates** to release a **free uncharged base**, which is lipid soluble. It can pass via the lipid cell membrane to the interior of the axon.

N.B.: pKa is the pH at which the amounts of ionized and non-ionized drug are equal.

The relative proportion of charged and uncharged local anesthetics is determined by the pKa of the drug (each drug has its own pKa) and the environmental pH (e.g., the pH of the tissues which is usually 7.4).

• Inside the axon, re-equilibrium occurs where some of the uncharged molecules change to ionized molecules i.e., **re-ionization**. The re-ionized forms enter Na^+ channels and block them.

- Actually, because re-ionization occurs intracellularly, individual drug pKa has a little effect on the rate of onset of blockade.

- The drug also enters capillaries and is removed by the circulation. Eventually, tissue concentration decreases below that in the nerves. The drug diffuses out and restoration of normal function occurs.

2- Some local anesthetics may penetrate the axonal membrane causing **membrane expansion**; therefore, **distortion and constriction of Na^+ channels** occur. It is analogous to the critical volume hypothesis of general anesthetics e.g., benzocaine.

3- Surface charge theory: some local anesthetics may partially penetrate the axonal membrane leading to an increase in the trans-membrane potential resulting in inhibition of depolarization.

Other Actions of Local Anesthetics (besides the blockade of Na^+ channels)

1- Blockade of Ca^{++} and K^+ channels.

2- Blockade of N-methyl-D-aspartate (NMDA) receptors.

Both 1 and 2 can explain the differences between local anesthetics in their efficacy and toxicity.

3- Impairment of axoplasmic transport.

4- Blockade of transduction of mechanical stimuli in nociceptors.

5- Impairment of leukocyte and monocyte functions, resulting in inhibition of chemotaxis, and reduction of free radical production.

6- Neuronal injury.

Other Local Anesthetic Drugs:

Many other drug groups and substances can block sodium channels and have local anesthetic actions such as:

- Tricyclic antidepressants (amitriptyline).

- Meperidine.

- Volatile anesthetics.

- Ketamine (besides its NMDA blocking action).

- Tetrodotoxin and saxitoxin (they are poisons found in puffer fishes and can block sodium channels from outside the cell membrane).

- Capsaicin (the pungent ingredient found in Chilli peppers, it has a selective sensory block action without motor action).

These drugs are still under research in rats to be used as new long acting local anesthetics.

Frequency-Dependent or Use-Dependent Block (Phenomenon)

Definition:

Local anesthetic inhibition of sodium channels and subsequent sodium influx increase with repetition of depolarization and nerve stimulation.

Explanation:

Voltage-gated sodium channels are membrane-bound proteins existing in 3 forms; resting (i.e., not sharing in the process of action potential), activated (i.e., open during action potential allowing sodium influx), and inactivated (i.e., closed after opening at the end of action potential).

Local anesthetics have a much greater affinity and bind more readily to the channel in the activated and inactivated forms than in the resting form. Repeated nerve stimulation and action potentials increase the number of sodium channels that are activated and inactivated; therefore, local anesthetic action on the sodium channels is greatest when the nerve is firing repeatedly.

Structure-Activity Relationship

Local anesthetics consist of:

1- Aromatic Group (Benzene Ring):

It determines: • **fat solubility** and so the **potency** (lipophilic group).

- **duration of plasma protein binding** as Na^+ channel is protein in nature, so drugs that bind to proteins for a longer time, have a longer duration of action.

2- Tertiary Amine Group:

It determines **water solubility** at the physiological pH. Tertiary amines usually carry positive charges, so they are weak bases.

3- Intermediate Chain:

It is the basis for local anesthetic classification (figure 3-27).

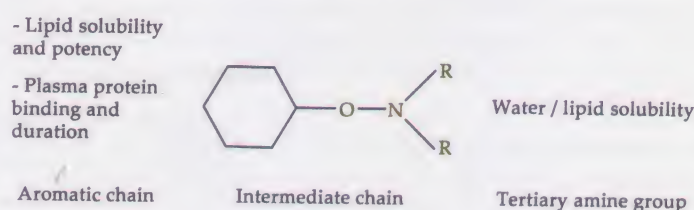


Figure 3-27: Structure of local anesthetics

It is either: • amino-amine local anesthetics (with amide linkage) or
• amino-ester local anesthetic (with ester linkage).

It determines the difference between the esters and amide types (see later).

Q: Discuss structure-activity relationships of different anesthetic agents?

Potency

It depends on:

- 1- Lipid solubility: as **increased lipid solubility** is associated with increased potency.
- 2- Molecular weight: as **increased molecular weight by increased number of carbon atoms** in the molecule is associated with increased potency.

For example,

- adding a butyl group to mepivacaine (less potent) results in bupivacaine (which is more potent).
- adding a halide group to procaine results in 2-chloroprocaine (which is relatively less toxic due to rapidly hydrolysis).

Relative Potency is Measured by:

a. The Minimum Local Anesthetic Concentration (C_m or MLAC):

It is the minimum concentration of local anesthetic that will block nerve impulse conduction (it is analogous to the MAC of inhalational anesthetics).

Or it is the median effective local anesthetic concentration in a 20 mL volume for epidural analgesia in the first stage of labor.

b. The Minimum Effective Anesthetic Concentration (MEAC):

It is the concentration at which a spinal anesthetic agent produces surgical anesthesia within 20 minutes of administration in 50% of patients.

None of MLAC or MEAC is used clinically.

Potency is Affected by:

1- Fiber size, type and myelination:

- The small unmyelinated fibers (e.g., sensory "C" fibers) are blocked more rapidly by most local anesthetics than large myelinated fibers (motor "A" fibers).
- In terms of absolute sensitivity, large diameter fibers are more sensitive than small ones, but usually large fibers are myelinated which act as a barrier to drug diffusion.

2- pH: as **acidic pH antagonizes** the block because acidosis decreases the free bases and increases the ionized forms.

3- Frequency of nerve stimulation (use-dependent block phenomenon): discussed above.

4- Electrolyte concentration; **hypokalemia** and **hypercalcemia** antagonize blockade.

Speed of Onset of Action

It depends on:

1- pKa of the Drug:

The pKa of the drug is the pH at which the amount of ionized form will equal the amount of the non-ionized form, but the drugs act in the tissues or blood where the physiological pH is different from the pKa (i.e. 7.4); therefore, the amount of the ionized and the non-ionized forms will not be equal at this physiological pH.

If the pKa of the drug is the same as the physiological pH (7.4), the amount of the ionized and non-ionized forms will be equal (50% for each).

If the pKa of the drug is closer to the physiological pH (7.4), both the ionized and non-ionized fractions will be available in considerable amounts.

Both ionized and non-ionized forms of the drugs are important for the rapid action of the local anesthetics because the non-ionized form is the form that penetrates and diffuses through the cell membrane while the ionized form is the one that binds to the receptors. If one form is present in excess to the other form, the action will be delayed.

Local anesthetics have higher pKa than the physiological pH; therefore, their non-ionized fraction is present in small amounts. The local anesthetics with pKa closer to the physiologic pH i.e., decreased pKa will have a higher concentration of non-ionized free base that can pass through the nerve cell membrane. Once inside the nerve cells, the non-ionized base reaches equilibrium with its ionized form. After that, the ionized form binds and blocks sodium channels and produces the action at a more rapid onset.

For example, lidocaine has a more rapid onset of action (its pKa is 7.8) than bupivacaine with pKa 8.1.

Therefore,

- Commercially prepared drugs are usually prepared in acidic media (by adding HCl) to increase their water solubility and become easily diluted in normal saline, but this acidic medium delays the onset of action and if the drug is injected in infected (acidic) tissues, a more delayed onset occurs.
- If carbonated solutions of local anesthetics rather than HCl salts are used, rapid onset occurs due to improved intracellular distribution of the ionized form.
- Alkalinization of local anesthetics by adding NaHCO_3 (e.g., 1 mL 8.4% NaHCO_3 per 10 mL 1% lidocaine) produces a more rapid onset and improves the quality of the block due to the increased amount of free base available.

2- Molecular Weight of Local Anesthetics:

Local anesthetics with low molecular weight have a more rapid onset of action.

Spread of Local Anesthetics after Injection:

The fibers of a mixed peripheral nerve e.g., upper limb nerves, are distributed inside the nerve as the fibers that supply the proximal areas e.g., shoulder are present in the mantle of the nerve; whereas the fibers that supply the distal areas e.g., wrist are present in the core of the nerve fibers. This anatomic arrangement accounts for the initial proximal anesthesia with subsequent distal anesthesia as the local anesthetic diffuses from the mantle to the central core of the nerve (figure 3-28).

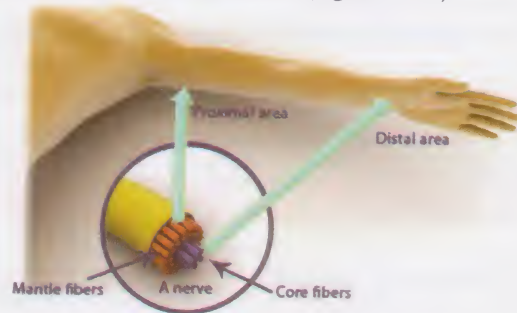


Figure 3-28: Distribution of fibers in a peripheral nerve

Duration of Action

It depends on the **aromatic group** which determines the **lipid solubility** which in turn, determines the duration of **plasma protein binding**.

As increased lipid solubility is associated with increased plasma protein binding in blood, this decreases the clearance of local anesthetics. Also, Na^+ channels are protein in nature; therefore, drugs bind to proteins (and Na^+ channels) for a longer time and become retained within the nerve resulting in a longer duration of action.

New Techniques Allowing Slow Release Preparations (e.g., for bupivacaine)

1- Lipid Emulsions:

The rationale for development of lipid emulsions of local anesthetics is based on the relative solubility of the ionized and free based forms of bupivacaine in aqueous and lipid solutions. Ionization causes slow release of the active drug. Therefore, formulation of bupivacaine in an **emulsion** of soya bean oil, triglycerides and egg lecithin **increases the ionized form and so the duration of action is prolonged**.

2. Liposomes:

They are **bio-degradable lipid molecules** with a polar head and two hydrophobic hydrocarbon tails which form lipid bi-layers like a cell membrane. Incorporation of bupivacaine **inside liposomes** allows bupivacaine to **remain at the site of action** for a more prolonged period and causes **slow release of the drug** prolonging the duration of action.

3. Polymer Microspheres:

They are **biodegradable** polylactic and lactic-glycolic acid **polymers** in which the drug is incorporated inside causing prolongation of the duration of action.

4. **Suspensions:** Suspension of local anesthetics in polysorbate-80 causes slow continuous dissolution which prolongs the duration of action.

Tachyphylaxis

It is the decrease of efficacy of repeated doses due to the eventual consumption of local extracellular buffering capacity by the acidic local anesthetics.

Pharmacokinetics

Absorption:

Factors Affecting Systemic Absorption:

1- The site of injection:

• Increased **vascularity** at the site of injection results in increased systemic absorption and, so increases systemic toxicity. The routes are arranged from the highest absorption capacity to the lowest; **i.v.** > **tracheal** > **intercostal** > **caudal** > **paracervical** > **epidural** > **brachial plexus** > **sciatic** > **subcutaneous** > **skin**.

2- Presence of vasoconstrictors:

• They decrease the absorption of local anesthetics and so decrease their systemic absorption and toxicity. For more details, see later.

3- The types of local anesthetics:

- Local anesthetics which are highly tissue-bound are more slowly absorbed e.g., etidocaine.
- Local anesthetics vary in their intrinsic vasodilator properties except **cocaine**, **prilocaine** and **ropivacaine** which have **vasoconstrictive action**.
- Local anesthetics with high potency are usually highly toxic.

Distribution:

- Local anesthetics bind to plasma proteins: - primarily to α_1 - acid glycoprotein.
and - secondarily to albumin.

Factors Affecting Distribution and Organ Uptake:

1- Tissue Perfusion:

The highly perfused organs e.g., brain, lung, liver, kidney and heart, have an initial rapid uptake (α phase) which is followed by a slower redistribution (β phase) to moderately perfused organs (as muscle and gut).

2- Tissue/Blood Partition Coefficient:

- Strong plasma protein binding retains local anesthetics in the blood, but this does not affect acute toxicity.
- High lipid solubility increases tissue uptake.

3- Tissue Mass:

- Muscles provide the greatest reservoir for local anesthetics due to their large mass.
- Fat provides also a great reservoir for local anesthetics due to the high affinity of these drugs to fat.

Metabolism and Excretion

	Esters	Amides
Metabolism	Rapidly by pseudo-cholinesterase to water-soluble metabolites that are excreted in the urine. So, patients with genetically abnormal pseudo-cholinesterase are at an increased risk of toxicity due to the slower rate of metabolism. N.B.: Cocaine is partially metabolized by the liver and partially excreted unchanged by the kidneys	Slowly by microsomal enzymes (amidases) in the liver So, their metabolism is decreased with increased toxicity in: - decreased hepatic function (cirrhosis) - decreased hepatic blood flow (congestive heart failure, general anesthesia, vasopressors, H_2 -receptor blockers as cimetidine or propranolol). N.B.: Prilocaine is metabolized to a greater degree by the lungs, but more rapidly by the liver.
Hyper-sensitivity	More common due to one of its metabolites, P-amino-benzoic acid (PABA) which is highly allergic.	Less common
Stability	Heat sensitive and tend to hydrolyze spontaneously on warming, so they have short shelf lives.	Heat insensitive , so they have long shelf lives (unless mixed with glucose to produce hyperbaric spinal solutions).

N.B.: • Termination of action of intrathecally-injected local anesthetics depends upon their absorption into the blood stream, where esters are hydrolyzed by pseudo-cholinesterase and amides are metabolized in the liver.

- Plasma protein binding does not affect acute toxicity of drugs.

Q: Compare esters and amides?

A: Discuss the cause of classification, differences in metabolism and excretion with examples.

Factors Increasing Systemic Toxicity of Local Anesthetics

1- The site of injection.

2- Presence of vasoconstrictors.

3- The type of the local anesthetic.

4- Decreased metabolism either by abnormal pseudo-cholinesterase or decreased hepatic metabolism.

All these factors are discussed above.

5- **Increased dose of the drug** causes a more rapid onset and a prolonged duration.

Increased dose occurs either by increasing the concentration or increasing the volume. A larger volume of a diluted solution is usually more effective.

6. The type of the patient:

Pregnant, short stature and elderly patients have increased segmental spread of extra-dural block.

Young, fit, alcoholic or anxious patients require more drugs.

Individual Local Anesthetic Drugs

A- Esters:

1. **Cocaine**: It has high toxicity and produces vasoconstriction. Its maximum safety dose for infiltration and blocks is 3 mg/kg.

2. **Benzocaine**: It has high protein binding, so it has a long duration.

3. **Procaine**: It has high lipid solubility, so it has high potency. Its maximum safety dose for infiltration and blocks is 6 mg/kg without adrenaline and 10 mg/kg with adrenaline. It is mainly used for spinal anesthesia.

4. **Chloroprocaine**: It has low toxicity, so its **maximum safety dose is 7.5 mg/kg without adrenaline and 12 mg/kg with adrenaline** because it is highly cleared by plasma esterases. It is mainly used for epidural anesthesia. It can be used in spinal anesthesia, but it should be preservative-free.

5. **Amethocaine (tetracaine)**: It is used mainly for spinal anesthesia (it cannot be used for epidural or peripheral nerve blocks due to its delayed onset). Its maximum safety dose is 1.25 mg/kg without adrenaline and 3 mg/kg with adrenaline.

B- Amides:

1. **Lignocaine or lidocaine (Xylocaine)**:

It has **medium** lipid solubility, so it has medium potency. Its pKa is 7.8.

It has medium protein binding, so it has a medium duration.

It has medium toxicity.

Its maximum safety dose for infiltration and blocks is **4.5 mg/kg without adrenaline and 7.0 mg/kg with adrenaline**. In tumescent anesthesia, lidocaine doses are larger e.g. 30-70 mg/kg; see later in chapter of "Plastic Surgery".

It is used in many local indications such as epidural, spinal, local infiltrations and peripheral nerve blocks. It is also used as an antiarrhythmic drug.

2. **Mepivacaine** or Carbocaine:

As lignocaine

3. **Bupivacaine (Marcaine)**:

It is the R-isomer of bupivacaine.

It has **high** lipid solubility, so it is highly potent. Its pKa is 8.1.

It has high protein binding, so it has a long duration.

It has more toxicity than lignocaine especially cardiovascular and central nervous system toxicity.

Its maximum safety dose for infiltration and blocks is **2 mg/kg without adrenaline and 3 mg/kg with adrenaline**.

It is used mainly for spinal, epidural, and peripheral nerve blockade.

N.B.: Levo-bupivacaine or **S-bupivacaine (Chirocaine)** is the S- isomer of bupivacaine. It is a new local anesthetic. It is less cardiotoxic than the R-isomer bupivacaine.

4. **Ropivacaine (Naropin)**:

As bupivacaine (chemically derived from bupivacaine) i.e., has high lipid solubility, high potency, long duration, high toxicity, and low maximum safety doses is 2 mg/kg without adrenaline and 3 mg/kg with adrenaline ; but

- Less cardiotoxic and has less central nervous system toxicity than R-bupivacaine (due to less lipid solubility).
- More vasoconstrictor action, so has a longer duration. Its pKa is 8.1.
- It produces **greater separation of sensory and motor** blockade, so it is the drug of choice for epidural use in obstetric and postoperative analgesia.
- Its ampoule is 10 mL (7.5 mg/mL) (0.75%). At this concentration, it acts motor and sensory. When

27.5 mL normal saline are added to the ampoule, 2 mg/mL (0.2%) is obtained which acts mainly on sensory fibers (figure 3-29).

3. Dibucaine:

It is highly toxic. It is used for detection of abnormal pseudo-cholinesterase.

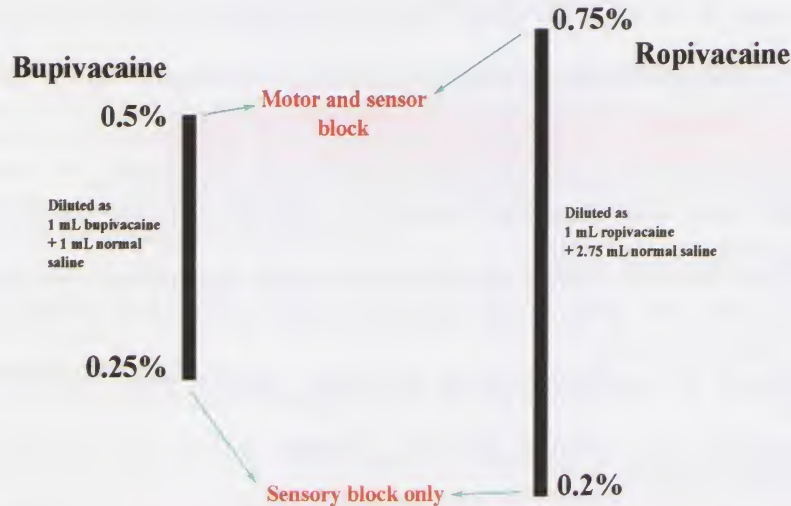


Figure 3-29: The differences in concentrations of bupivacaine and ropivacaine

4. Etidocaine:

It is highly toxic. Its maximum safety dose for infiltration and blocks is 3.5 mg/kg without adrenaline and 4.5 mg/kg with adrenaline. In contrast to other local anesthetics, it has a more profound effect on motor than on sensory fibers.

5. Prilocaine:

It has very low toxicity, so its maximum safety dose for infiltration and blocks is 4.5 mg/kg without adrenaline and 8 mg/kg with adrenaline. It is the best agent for intravenous regional anesthesia.

N.B.: The maximum safety doses are those used in infiltration and blocks. It is only a guide. Care should be taken according to the site of injection, the use of vasoconstrictors, and other factors increasing the systemic toxicity. The following table shows the maximum safety dose for infiltration and blocks:

Local Anesthetic Agent	Plain Without Adrenaline (mg/kg)	With Adrenaline (mg/kg)
Cocaine	2	3
Procaine	6	10
Chloroprocaine (the safest)	7.5	12
Amethocaine	1.25	3
Lignocaine	4.5	7
Mepivacaine	4.5	7
Bupivacaine	2	3
Ropivacaine	2	3
Etidocaine	3.5	4.5
Prilocaine	4.5	8

Q: Discuss ropivacaine?

A: The following points should be discussed:

- Mechanism of action.
- Chemical structure.
- Pharmacokinetics.
- Toxicity and side effects.
- Dose.
- Uses.
- Drug interactions.

Uses of Local Anesthetics

- 1- In regional and local anesthesia.
- 2- Systemic local anesthetics are used as analgesics for many forms of neuropathic pain e.g., lidocaine (intravenously or subcutaneously), or mexiletine (orally).
- 3- Lidocaine is used as an antiarrhythmic.
- 4- Lidocaine is also used to decrease the stress response to intubation and to decrease the intracranial tension.
- 5- Dibucaine is used to determine abnormal acetyl-cholinesterase enzyme.

Drug Interactions with Local Anesthetics

- 1- Non-depolarizing muscle relaxant blockade is potentiated by local anesthetics.
- 2- Succinylcholine and ester local anesthetics depend on pseudo-cholinesterase for their metabolism; therefore, both drugs potentiate each other.
- 3- Dibucaine inhibits pseudo-cholinesterase and it is used to detect a genetically abnormal enzyme.
- 4- Cimetidine, vasopressors, and propranolol decrease hepatic blood flow causing decreased lidocaine metabolism. This increases its toxicity.
- 5- Opioids (e.g., fentanyl or morphine) and α_2 -adrenergic agonists (e.g., clonidine) potentiate local anesthetic pain relief.
- 6- Epidural chloro-procaine may interfere with the analgesic actions of intra-spinal morphine (also, epidural bupivacaine and fentanyl).

Systemic Effects and Systemic Toxicity

Systemic effects include specific actions and toxic effects which are either local or systemic. Systemic toxicity is the toxic effects due to drug over-dosage only.

Causes: 1- Inadvertent intravascular injection (the most common cause).

2- Absolute over-dosage that exceeds the patient's body weight and general condition.

Factors Increasing Systemic Toxicity of Local Anesthetics: See above.

• Mixtures of local anesthetics should be considered to have roughly additive toxic effects e.g., a solution containing 50% of the toxic dose of lidocaine and 50% of the toxic dose of bupivacaine will have 100% of the toxic effects of either drug.

Clinical Picture of Toxicity:

1. Central Nervous Effects:

a) Toxicity:

- The **earliest** features are numbness and tingling of the tongue and circumoral area because these areas have very rich blood supply depositing large amounts of local anesthetic at these sites.
- Then **cerebral stimulation** occurs such as tinnitus, blurred vision, vertigo, restlessness, agitation, nervousness, muscle twitches, and tonic-clonic seizures up to convulsions. They are due to selective blockade of inhibitory GABA pathways, leaving excitatory NMDA pathways unopposed. This leads to **central nervous system dis-inhibition**.
- Finally, **cerebral depression** occurs such as slurred speech, drowsiness, unconsciousness up to respiratory arrest due to inhibition of both inhibitory and excitatory pathways with high doses.

b) Specific Effects:

- **Lidocaine** (i.v. 1.5 mg/kg) **decreases cerebral blood flow and intracranial pressure during intubation**.
- **Lidocaine 5%, tetracaine 0.5%, or chloro-procaine** (formulated with Na meta-bisulfite) on repeated doses via continuous spinal analgesia causes **cauda equina syndrome, transient neurologic symptoms, and persistent sacral root irritation** due to pooling of the drug around the cauda equina in high concentrations leading to permanent neuronal damage.

This **local neuro-toxicity** occurs more commonly with **small-gauge micro-catheters** than with conventional wide bore spinal needles because those catheters decrease the mixing of local anesthetic with cerebrospinal fluid exposing the nerve roots to relatively high concentration of local anesthetics.

- **Lidocaine and procaine infusions** decrease the MAC of inhalational agents by 40%; therefore, they are used to supplement anesthesia.
- **Cocaine** stimulates the central nervous system and usually causes a sense of euphoria.

2.3 Cardiovascular Effects:

a) Toxicity:

- Local anesthetics produce negative effects:

- Decreased myocardial automaticity (negative chronotropic effect).
- Decreased myocardial contractility (negative inotropic effects).
- Decreased conduction velocity (negative dromotropic effects).
- Decreased duration of the refractory period.
- Vasodilatation (except cocaine, prilocaine and ropivacaine, which cause vasoconstriction).

These effects result in bradycardia up to heart block and hypotension, ventricular tachycardia, Torsades de pointes, and ventricular fibrillation up to circulatory collapse.

- With the exception of bupivacaine, the systemic concentration of local anesthetic required to produce severe cardiovascular toxicity exceeds that of central nervous system toxicity; therefore, central nervous system toxicity occurs before cardiovascular toxicity.

Sometimes bupivacaine produces cardiovascular collapse without producing obvious signs of central nervous system toxicity first.

- Causes of cardio-toxicity:

1- Blocking cardiac Na⁺ channels:

The time that a local anesthetic agent occupies and blocks the cardiac Na⁺ channel is called the **Dwell time**.

- For **R- bupivacaine**, the Dwell time is **1.5 seconds** (i.e., relatively prolonged); therefore, R- bupivacaine does not have enough time to dissociate from Na⁺ channel during diastole (diastole = 0.40 sec). R- bupivacaine will accumulate causing more cardio-toxicity. Its cardiac arrest is difficult to resuscitate.
- The Dwell time for **S-bupivacaine** is **less** than R-bupivacaine, so less cardio-toxicity is produced).
- Ropivacaine has the shortest Dwell time, so; its cardio-toxicity is less than R- and S-bupivacaine.
- For **lidocaine**, the dwell time is **0.15 sec**. It has enough time to dissociate from Na⁺ channels during diastole causing less cardio-toxicity.

2- Inhibition of voltage-gated calcium channels.

3- Inhibition of ATP synthesis in cardiac fibers.

4- Inhibition of β_2 adrenergic receptors resulting in reduction of adenyl cyclase activity i.e., decreased intracellular cAMP.

5) Special Effects:

- **Lidocaine** - decreases the pressor response to intubation (1.5 mg/kg 1-3 min before intubation).
- has an **antiarrhythmic** effect against ventricular arrhythmias.
- Cocaine inhibits reuptake of norepinephrine after its release at the adrenergic nervous system, leading to adrenergic stimulation with hypertension, and ventricular arrhythmias. They are treated by adrenergic and calcium channel blockers.

3. Respiratory Effects:

- a) **Toxicity:** in large doses, **respiratory depression** up to arrest may occur.

b) Specific Effects:

- **Lidocaine depresses the hypoxic drive** (i.e., respiratory response to low PaO₂).
- Direct exposure to local anesthetics causes depression of the medullary respiratory center e.g., post-retrobulbar apnea syndrome.

Other Additional Side Effects:

1- Allergic Reactions:

- Occur more with **esters** than amides especially procaine due to production of **para-amino benzoic acid** which is a known allergen and produced only with esters.
- Amides rarely cause allergic reactions; mostly due to the preservative methyl paraben (its chemical structure is similar to p-amino benzoic acid).

There is no cross-sensitivity between classes of local anesthetics. If a patient is allergic to ester local anesthetic, amides can be given safely.

2- Musculoskeletal Effects (Myo-Toxicity):

- Direct injection into skeletal muscles e.g., injection of trigger-points in myofascial pain or injection in extra-ocular muscles during local anesthesia of the eye causes myofibril hyper-contraction which progresses to **lytic degeneration**, edema and necrosis. Regeneration usually occurs after 3-4 weeks.
- It is more common with 2-chloro-procaine and bupivacaine than procaine or ropivacaine.

3- Met-Hemoglobinemia:

- It is common with **benzocaine** and **prilocaine** (due to its metabolites *ortho*-toluidine derivatives).
- Fetal Hb in neonates is more sensitive. It is better to avoid prilocaine in epidural anesthesia during labor.

4- Reduction of Coagulation:

Lidocaine decreases coagulation by prevention of thrombosis and decreased platelet aggregation with increased fibrinolysis, detected by thrombo-elastography. This explains failure of the epidural autologous blood patch shortly after local anesthetic injection.

Prevention of Systemic Toxicity:**1- The single most important factor is avoidance of accidental intravascular injection:**

- Careful **aspiration tests** should be repeated each time the needle is moved and after each 5-10 mL of solution.
- **Initial** injection of 2-3 mL of **solution containing adrenaline** 1:200 000 is mandatory. If there is an increase in the heart rate within 1-2 min, intravascular injection is expected.
- **Injection should be done slowly.**
- Careful patient observation for **early signs of toxicity** is important. Injection can be stopped before occurrence of major toxicity.

2- Avoidance of over-dosage:

- Consideration of the behavior of various drugs after injection at a particular site should be in mind.
- The appropriate drug and dose for each block should be chosen carefully.
- Maximum safety dosage should be considered (with or without adrenaline).
- Patient's general condition should be evaluated.
- Concomitant use of general anesthesia is an important factor.

Treatment of Toxicity:

Facilities for treatment and resuscitation must always be available before doing the block.

Treatment is mainly **supportive treatment**;

1. Stop injecting the local anesthetic.

2. Call for help.

3. Respiratory support:

- **Airway** must be maintained and oxygen supply by a face mask up to artificial ventilation should be applied if necessary as in case of apnea.
- Some authors recommend considering **hyperventilation** to reduce PaCO₂. This helps reduction of cerebral blood flow which in turn decreases delivery of local anesthetics to the brain and correct the pH in case of metabolic acidosis.

4. **Neurological support: convulsions** should be **treated** by small increments of diazepam 2.5 mg, 1-2 mg/kg i.v. thiopental (more available in operating theaters), or i.v. propofol.

5. Cardiovascular support:

- **Ventricular arrhythmias:** Some authors recommend **amiodarone** over lidocaine. Although lidocaine is the traditional first-line drug in management, there is a controversy to use one local anesthetic to treat toxic systemic effects of another as lidocaine may increase the cardio-toxicity.
- **Hypotension:** can be treated by adrenergic drugs with α and β agonists e.g., **ephedrine 5 mg increments.**

- **Cardiovascular collapse and arrest:** Start cardiopulmonary resuscitation (CPR) using standard protocols. **Cardiac arrest due to bupivacaine toxicity** is usually **resistant** to epinephrine and even lethal ventricular tachyarrhythmias may occur with epinephrine; therefore, some authors recommend norepinephrine or vasopressin in cardiac resuscitation. Lipid therapy can be used in cardiac arrest.

- **Lipid Therapy (Lipid-Based Resuscitation):**

Lipid infusion either prophylactic (before bupivacaine toxicity) or therapeutic (after bupivacaine asystole) can improve the results and protect the cardiovascular system from bupivacaine toxicity.

Mechanisms: There are 4 theories:

1- Lipid infusion accelerates the washout of local anesthetics from the myocardium because lipid emulsion in blood will draw and segregate uncharged lipophilic bupivacaine molecules from the hydrophilic plasma, which makes them unavailable for interaction at the myocardium and extracts bupivacaine from the cardiac cells, thus promoting successful resuscitation.

2- Lipid or its components of fatty acids may interact with bupivacaine at the tissues.

3- Lipid infusion may help restore myocardial ATP stores depleted by bupivacaine toxicity.

↳ Lipid infusion accelerates nitric oxide production and reverses bupivacaine's inhibition of nitric oxide synthesis. Inhibition of nitric oxide increases bupivacaine cardio-toxicity.

Dose of Intralipid:

Lipid therapy should be initiated at the earliest sign of severe local anesthetic-induced cardiac toxicity.

Intralipid 20% should be given intravenously in the following regime:

- Intralipid 20% 1.5 mL/kg over 1 min (2 x 50 mL for a 70 kg adult).
- Follow immediately with an infusion at a rate of 0.25 mL/kg/min (17.5 mL/min for a 70 kg adult).
- Continue chest compression (lipid must circulate) if appropriate.
- Repeat 1.5 mL/kg bolus once or twice if no improvement occurs (2 x 50 mL for a 70 kg adult).
- Continue infusion until hemodynamic stability is restored. Increase the rate to 0.5 mL/kg/min if blood pressure declines (35 mL/min for a 70 kg adult).
- A maximum total dose of 8 mL/kg is recommended (560 mL for a 70 kg adult).

Remember:

- Continue CPR throughout treatment with lipid emulsion.
- Recovery from local anesthetic-induced cardiac arrest may take >1 h.
- Propofol is not a suitable substitute for Intralipid®. Although some propofol preparations are provided in Intralipid®, e.g., Diprivan®, these are not a suitable alternative, due to the significant cardiovascular depression caused by propofol. This does not preclude the use of small incremental doses of propofol to control seizures.

In the Future:

- Researches are directed to produce drug scavenging nano-particles for the management of bupivacaine cardio-toxicity.
- Reducing the size of particles used to segregate bupivacaine and other sodium channel blockers as amitriptyline toxicity will increase their numbers and increase the surface area available to extract bupivacaine from the blood. This improves efficiency of management of bupivacaine's cardiac toxicity significantly.
- For example, oil-in-water emulsion-based nano-particles with diameters of 15-120 nm are more efficient than intralipid particles with diameters of 400-n.

N.B.: Nanotechnology

The word nanoscience originates from the Greek root "nanos" (i.e., dwarf) and has been adopted by the International System of Units (SI) to modify measurement units by 10^{-9} .

Nanoscience is the study, development, and use of matter at the nanometer scale (1 to 100 nanometer).

Engineers and others have reduced the size of objects from micrometer to nanometer. Chemists and others have worked to develop mechanisms for individual molecules to self-assemble into nano-particles.

Nanoscience is a fundamentally novel way of using matter because, at nano-meter size, matter develops unique previously unrecognized properties. For example, the interaction of nano-meter-sized particles with each other or with their environment is primarily influenced by surface tension and local electromagnetic effects, rather than by gravity or electrostatic forces.

Additives

a) For Pharmaceutical Purposes:

1. Na hydroxide and HCl acid; to adjust pH.
2. Na chloride; to adjust tonicity.
3. Glucose and water; to adjust baricity.

Heavy bupivacaine (*Heavy Marcaine*) is bupivacaine mixed with 8% glucose.

4. Preservatives; to kill bacteria such as:

- methyl hydroxyl benzoate.
- sodium bisulfate (neurotoxic) or a derivative of di-sodium ethylene-diamine-tetra-acetic acid (EDTA) (causes back pain). They are used with chloro-procaine.

Local anesthetics with preservatives should not be used for subarachnoid or epidural block.

5. NaHCO_3 ; to speed the onset. Some researches showed that it had no effect especially with lidocaine.

b) For Pharmacological Purposes:

1) Vasoconstrictors:

Value: Vasoconstriction decreases the rate of systemic absorption; therefore,

- It **decreases systemic toxicity**, so the dose can be increased safely by 50-100%.

• It increases the duration and intensity of block especially for short acting drugs e.g., lidocaine, but the addition of epinephrine to long acting drugs e.g., bupivacaine does not produce significant effects because the long duration of bupivacaine is due to its high degree of protein binding.

Epinephrine can also potentiate the analgesia by its α_2 -adrenergic action.

Agents: 1- Adrenaline: is the most potent and the most commonly used.

2- Noradrenaline.

3- Phenylephrine.

4- Felypressin: it is safe for dental use, but may cause coronary vasoconstriction.

Dose: Adrenaline concentration should not exceed 1: 200 000 (i.e., 1 mg diluted in 200 mL)

Maximal dose: should not exceed 0.5 mg.

N.B.: 1: 200 000

i.e., 1 g: 200 000 mL (because 1 g is equivalent to 1 mL)

i.e., 1000 mg diluted in 200 000 mL

i.e., 1 mg diluted in 200 mL

Contraindications:

1- Injection close to end arteries e.g., ring block of digits or penis.

2- I.v. regional anesthesia.

3- Theoretically, increased risk of permanent neurological deficit, as they render nerve tissues ischemic.

4- Cardiac patients: due to systemic effects of vasoconstrictors.

5- Interaction with other sympathomimetic drugs including tricyclic antidepressants and adrenergic drugs.

2) CO₂:

Many local anesthetics are commercially produced as carbonated salts with CO₂ dissolved under pressure in the solution. Therefore, after injection, CO₂ decreases intracellular pH that increases the ionized active form of the drug speeding up the onset of the block.

3) Dextrans:

Mixing local anesthetics with high molecular weight dextrans (especially with adrenaline) produces macromolecules which hold local anesthetic molecules in tissues for longer periods. This increases the duration of action.

4) Hyaluronidase:

It is used to break down tissue barriers, aiding the spread of local anesthetics e.g., during ophthalmic local anesthesia.

5) Mixtures of Local Anesthetics:

- For example, lidocaine and bupivacaine mixture.

Advantages:

- To achieve the rapid onset of lidocaine and the long duration of bupivacaine, but some researches concluded that unpredictable blockade characteristics might occur.
- To decrease toxicity, but actually local anesthetic toxicity is additive so that the use of 50% of doses of both local anesthetics can cause 100% of the toxic effects of either drug.

6) Other Analgesic Drugs can be mixed with the Local Anesthetics during Spinal or Epidural Anesthesia:

For example:

• Opioids (morphine, pethidine or fentanyl):

They can increase the duration and intensity of local anesthetic action.

• Clonidine: (15-50 µg in spinal anesthesia and 50-120 µg in epidural anesthesia).

- It speeds the onset and prolongs the duration of the block.
- It produces a dose sparing effect of local anesthetics.
- It decreases shivering during regional anesthesia.
- It produces sedation, but hypotension may occur.

• Neostigmine: (10-100 µg in spinal anesthesia)

- It may increase the duration of the block.
- It causes nausea and vomiting.

• Midazolam:

- 2 mg preservative-free intrathecal midazolam enhances the analgesic effect of fentanyl.

- The formulation of midazolam, commercially available in many countries such as US and Egypt, is not preservative-free and; therefore, should not be used intrathecally as it may present a risk of neurotoxicity.
 - **Ketorolac.**
 - **Ketamine (0.4 mg for each mL of epidural solution) (0.5 mg/kg).**
- All drugs added to local anesthetics in spinal or epidural anesthesia should be preservative free drugs. For more details about intrathecally and epidurally injected drugs, see chapter of "Pain Management".

EMLA Cream

It is Eutectic (easily melted) Mixture of Local Anesthetics (EMLA).

It consists of 1:1 mixture of unionized forms of 5% **lidocaine** and 5% **prilocaine** (by other authors, 2.5% lidocaine and 2.5% prilocaine) as oil in water emulsion. This mixture has a lower melting point than either component, and it exists as oil at room temperature that is capable of overcoming the barrier of the skin.

Onset: 1 hour.

Duration: 1-2 hours.

Pharmacokinetics:

- The depth of penetration is 3-5 mm.
- The amount of drug absorbed depends on:
 - The drug: - Application time.
 - Total dose administered.
 - The skin: - Keratin thickness.
 - Dermal blood flow.

Pharmacological Actions and Uses:

It produces dermal analgesia sufficient for:

- 1- L.v. line insertion especially in pediatric patients.
- 2- Split-thickness skin graft harvesting.
- 3- Laser removal of port-wine stains.
- 4- Lithotripsy because the pain originates as the sound waves pass through the skin.
- 5- Circumcision.

Side Effects:

Skin blanching, erythema, and edema.

Contraindications:

- 1- Application on mucous membranes or broken skin as great absorption occurs causing met-hemoglobinemia.
- 2- Infants less than one month old.
- 3- Patients with predisposition to met-hemoglobinemia (due to prilocaine).

Dose:

- It is applied 1 hour before the procedure and should be covered by a piece of non-absorbable covering during this hour, so as not to be wiped.
- 1-2 g of cream applied per 10 cm² area of skin.
- Maximum application area is 2000 cm² in adult.
- 100 cm² in children (< 10 kg).

Other New Local Anesthetic Creams

- 1- **ELA-Max (LMX):** 4% topical lidocaine.
- 2- **TAC:** tetracaine 0.9%, adrenaline 1: 200 000, cocaine 4-7%.
- 3- **Amethocaine gel or cream (Ametop):** It is similar to EMLA, but acts more quickly (within 30-45 minutes) and causes vasodilatation, which aids venous cannulation.
- 4- **S-Caine patch:** is a eutectic mixture of 70 mg of lidocaine and 70 mg tetracaine in a bio-adhesive layer that contains a heating element. A 20-minute application time is needed to produce analgesia for venipuncture procedures.

Ethyl Chloride (Chloroethane)

- It is a clear fluid, which boils at 12.5 °C and is stored under pressure in containers.
- It is highly inflammable, so it must be handled with care even if it is not used at all.
- Spraying the liquid on the skin causes rapid cooling and freezing of the surface.
- In the past, ethyl chloride was used for incision of paronychias and small abscesses, but it rarely provides adequate anesthesia and is not recommended.

Q: Discuss the new advances in local anesthetics?

A: The following subjects should be discussed:

- S-bupivacaine.
- Ropivacaine.
- Preservative-free chloroprocaine that has recently been developed.
- Other drugs with local anesthetic action such as ketamine, amitriptyline, tetrodotoxin, saxitoxin, and capsaicin (see before).
- New techniques allowing slow release preparations (see before).

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PHARMACOLOGICAL ADJUNCTS TO ANESTHESIA & INTENSIVE CARE

4

- Autonomic nervous system
- Drugs acting on the cardiovascular system
- Drugs acting on the respiratory system
- Drugs used in renal diseases
- Gastrointestinal drugs
- Hematological drugs

- Drugs acting on the central nervous system
- Chemotherapy
- Pharmacogenomics
- Drug chirality (isomerism) and anesthesia
- Drugs used during pregnancy

AUTONOMIC NERVOUS SYSTEM

Physiological Considerations

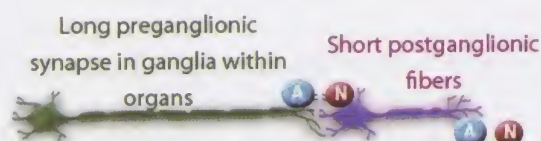
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The term autonomic nervous system refers to the nervous and humoral mechanisms which modify the function of the autonomous or automatic organs such as the heart, blood vessels, eye, liver, and kidneys...etc. The function of the autonomic nervous system is under control of two main divisions, the sympathetic and parasympathetic nervous systems.

The following figure (figure 4-1) explains origins, synapses, receptors, and neurotransmitters of the autonomic nervous system and somatic motor nerves.

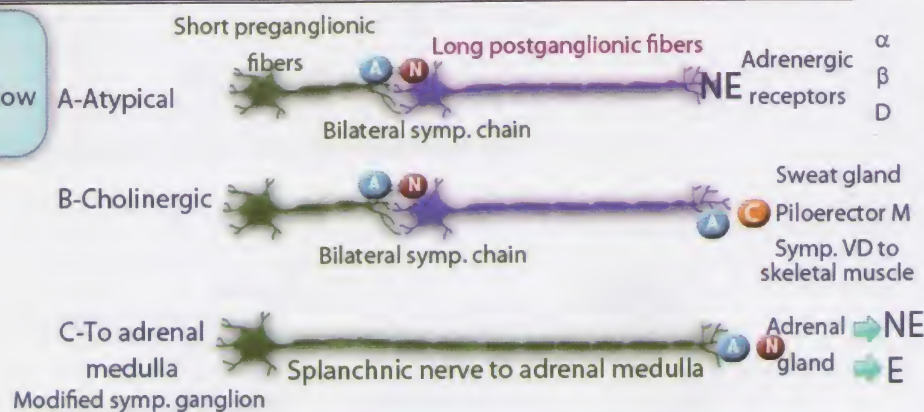
Parasympathetic System

Cranial nerves III-VII-IX-X
Sacral segment of spinal cord



Sympathetic System

Thoracolumbar outflow
from T1-L2



Somatic motor



- A AcetylCholine N Nicotinic receptors C Cholinergic receptors
NE Norepinephrine E Epinephrine

Figure 4-1: Autonomic nervous system

The Sympathetic Nervous System

Origin: It originates from the spinal cord, from T₁ to L₂ i.e., **thoracolumbar segments or outflow**. Each organ receives its sympathetic supply according to its embryological origin. For example, sympathetic supply of:

- the heart arises from T₁ to T₄ or T₅ (to a lesser extent),
- the neck arises from T₂,
- the chest arises from T₃-T₆,
- the abdomen arises from T₇-T₁₁.

Synapses:

There are 3 types of the sympathetic fibers:

a- Typical Nerves:

- They have short preganglionic fibers that synapse bilaterally in the sympathetic chain through acetylcholine (ACh) neurotransmitter which acts on nicotinic receptors.
- The postganglionic fibers are long fibers and reach most of the organs where they release norepinephrine (noradrenaline) that acts on adrenergic receptors (α and β types) or dopamine that acts on dopaminergic receptors (DA).

b- Cholinergic Nerves:

- The preganglionic fibers synapse bilaterally in the sympathetic chain through ACh neurotransmitter which acts on nicotinic receptors.
- The postganglionic fibers release ACh that acts on muscarinic receptors. They supply mainly sweat glands, vasodilator fibers in skeletal muscles, and piloerector muscles.

c- Splanchnic Nerve to the Adrenal Medulla:

- It contains preganglionic fibers that supply the adrenal medulla and release ACh that acts on nicotinic receptors. There are no postganglionic fibers. The adrenal medulla is considered a modified sympathetic ganglion.

Neurotransmitters

Epinephrine (adrenaline), norepinephrine (nor adrenaline), and dopamine are called catecholamines because they contain a catechol nucleus (figure 4-2).

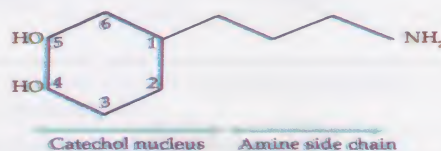


Figure 4-2: The standard structure of catecholamines

Synthesis:

The steps of catecholamine synthesis are discussed in figure 4-3.

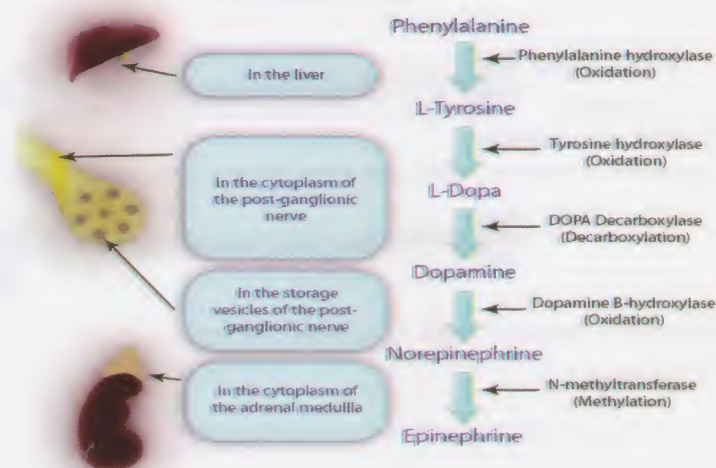


Figure 4-3: Catecholamine synthesis

Termination of Catecholamines:

The released neurotransmitters are terminated by one of the following ways:

1- Reuptake:

- Neuronal reuptake (uptake I, amine pump): norepinephrine is actively re-transported into the neuronal cytoplasm.
- Non-neuronal reuptake (uptake II): norepinephrine and epinephrine are taken into glial, muscle and endothelial cells where they are destroyed.

2- Diffusion from the receptor sites

3- Enzymatic catabolism:

There are two enzymes that metabolize catecholamines to inactive metabolites: Monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) (figure 4-4).



Figure 4-4: Metabolism of catecholamines

Adrenoceptors and Dopaminergic Receptors

	Alpha (α) receptors		Beta (β) receptors			Dopamine receptors	
	α ₁	α ₂	β ₁	β ₂	β ₃	DA ₁	DA ₂
Mechanism	Via G _q	Via G _i	Via G _s	Via G _s	Via G _s	Via G _s	Via G _i
Site	• Post-synaptic: in smooth muscle contraction of the eyes, blood vessels, lung, gut, and genitor-urinary tract.	• Presynaptic: causes decreased norepinephrine release (negative feedback) i.e., inhibition of sympathetic outflow. • Postsynaptic: - Vaso-constriction of blood vessels. - Aggregation of platelets. - Inhibition of fat cell lipolysis. - Sedation and inhibition of sympathetic outflow from the central nervous system.	• Post-synaptic: - Heart stimulation. - Kidneys: release of renin.	• Presynaptic: - Increased neuronal norepinephrine release (positive feedback). • Post-synaptic: - Vaso-dilatation of blood vessels. - Broncho-dilatation. - Decreased platelet aggregation. - Increased secretion of glands. - Heart stimulation.	• Post-synaptic: - Heart inhibition. - Increased lipolysis in fat cells.	• Post-synaptic: - Vaso-dilatation: of renal, splanchnic, coronary, and cerebral vessels. - Renal tubules: inhibition of sodium re-absorption leading to natriuresis and diuresis	• Presynaptic: in sympathetic nerves and adrenal medulla resulting in decreased dopamine release (negative feedback). • Post-synaptic: - CNS: Its stimulation causes vomiting (chemoreceptor trigger zone) and psychosis. Its inhibition causes depression, Parkinsonism, and galactorrhea.
Agonist	• Epinephrine. • Norepinephrine • Dopamine.		E = NE > isoprenaline > dopamine	Isoprenaline > E > NE > dopamine		• Dopamine • Bromocriptine (Parlodel). • Piribedi (Trivestral). • Morphine. • Fenoldopam. • Dopexamine.	
Non-selective							
Selective	• Phenylephrine. • Methoxamine	• Clonidine. • Dex-medetomidine.	Dobutamine Prenalatorol	Albuterol Fenoterol Retodrine Salbutamol Terbutaline			
Antagonists	Phentolamine	Tolazoline	Beta blockers			• Metoclopramide. • Methylergonovine • Antipsychotic drugs.	
Non-selective							
Selective	Prazosin Phenoxybenzamine	Yohimbine					

Mechanism of Adrenoceptor Action

• β and DA_1 receptors stimulate stimulatory guanine nucleotide binding proteins (Gs-proteins) which stimulate adenylate cyclase enzyme, increasing intracellular cyclic adenosine monophosphate (cAMP) (a 2nd messenger). This in turn stimulates intracellular enzymes such as protein kinase (a 3rd messenger) that produces the action (figure 4-5). They are called metabotropic receptors.

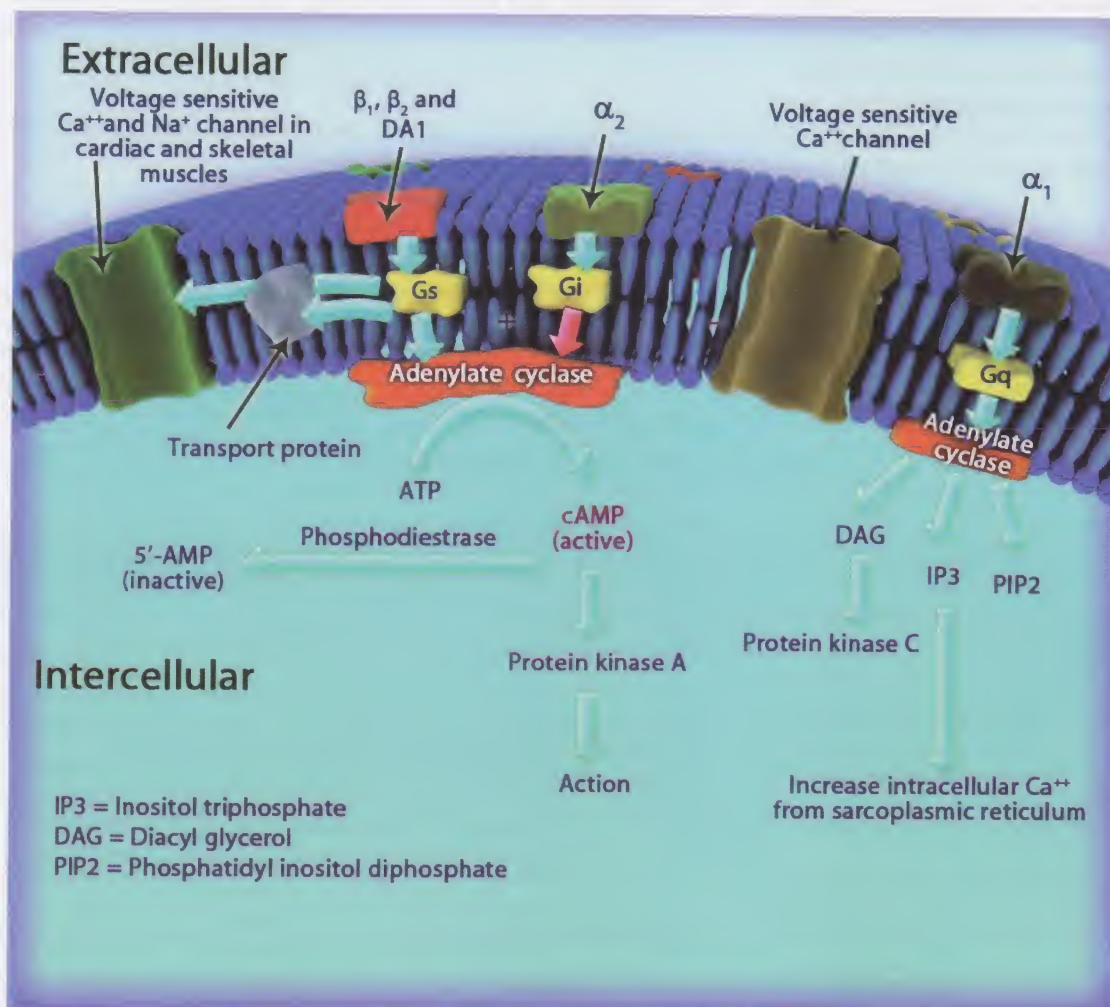


Figure 4-5: Mechanism of action of adrenoceptors.

Gs protein stimulates also voltage dependent calcium and sodium channels in skeletal and cardiac muscles.

• α_2 and DA_2 receptors stimulate inhibitory protein (Gi-protein) which in turn inhibits adenylate cyclase and decreases the intracellular cAMP.

Gi-protein inhibits also voltage dependent calcium channels.

• α_1 receptors stimulate Gq-protein which stimulates phospholipase C (PLC) that changes phosphatidyl inositol biphosphate (PIP_2) to inositol triphosphate (IP_3) and diacyl glycerol (DAG). IP_3 increases intracellular calcium from sarcoplasmic reticulum while DAG stimulates protein kinase C to produce the action.

N.B.: Ionotropic receptors act directly on ion channels such as sodium, potassium, or calcium channels.

The Parasympathetic System

Origin

• It arises from cell bodies of the motor nuclei of cranial nerves III, VII, IX, and X in the brain stem and from the sacral segments of the spinal cord i.e., **the cranio-sacral outflow**.

- As the majority of all parasympathetic nerves are contained in branches of the vagus nerve, which innervates the viscera of the thorax and abdomen, increased parasympathetic activity is characterized by signs of vagal over-activity.

Synapse

- The preganglionic fibers are long and synapse in ganglia within the organ innervated. The neurotransmitter released is ACh. It acts on nicotinic receptors.
- The postganglionic fibers are short and release ACh that acts on muscarinic receptors.

Neurotransmitters

Synthesis:

The steps of acetylcholine synthesis are discussed in figure 4-6.

Fate of ACh

ACh is hydrolyzed by cholinesterase enzyme (true and false). See before in the chapter of pharmacology of anesthesia.

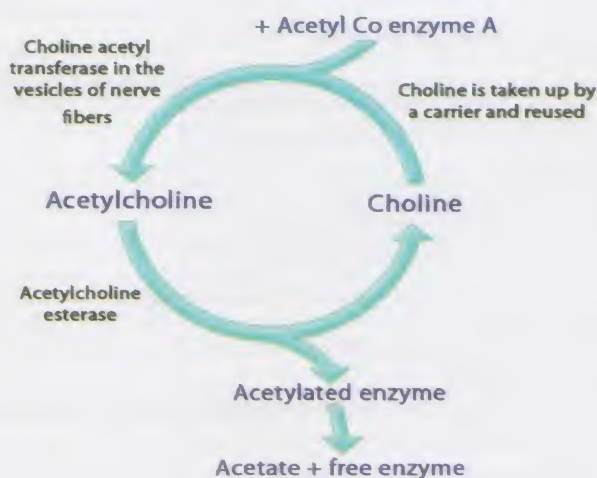


Figure 4-6: Synthesis of acetylcholine

Cholinergic Receptors

	Nicotinic Receptors	Muscarinic Receptors
Site	<p>a- Neuronal receptors: in</p> <ul style="list-style-type: none"> • Autonomic ganglia (sympathetic and parasympathetic). • Adrenal medulla. • They are excitatory in central nervous system. <p>b- Muscular receptors: in</p> <ul style="list-style-type: none"> • Neuromuscular junction. <p>They are ion-gated receptors (see before in the chapter of pharmacology of anesthesia).</p>	<p>There are 5 types:</p> <p>1- M₁: (acts via Gq-protein): in</p> <ul style="list-style-type: none"> • Autonomic ganglia. • Gastric parietal cells, resulting in increased gastric acid secretion. • They are excitatory in the central nervous system. <p>2- M₂: (acts via Gi-protein): in</p> <ul style="list-style-type: none"> • The heart, resulting in bradycardia. • Presynaptic cholinergic fibers, resulting in decreased ACh release. • They are inhibitory in the central nervous system. <p>3- M₃: (acts via Gq-protein) in</p> <ul style="list-style-type: none"> • Smooth muscles of the eyes, bronchi, gastrointestinal tract, urinary bladder, and blood vessels. • Lacrimal, salivary, gastric, and bronchial glands resulting in increased secretion. <p>4- M₄: (acts via Gi-protein) in</p> <ul style="list-style-type: none"> • Central nervous system. <p>5- M₅: (acts via Gq-protein) in</p> <ul style="list-style-type: none"> • Central nervous system.
Agonists	Non-selective: - Acetylcholine. - Nicotine.	Non-selective: - Acetylcholine. - Muscarine.
Antagonists	Neuronal: - dihydro-erythroidine. Muscular: - depolarizing and nondepolarizing muscle relaxants.	Non-selective: - Atropine. - Scopolamine. - Glycopyrrolate.

Actions of Sympathetic and Parasympathetic Systems

	Sympathetic System	Parasympathetic System (Muscarinic Actions)
Eye	<ul style="list-style-type: none"> • α_1: - Contraction of dilator pupillary muscles (Mydriasis). - Relaxation of ciliary muscle for far vision. • β_2: - Increased aqueous humor synthesis (increased intraocular pressure). 	<ul style="list-style-type: none"> • M: - Contraction of iris sphincter muscle (miosis). - Contraction of ciliary muscle for near vision (accommodation). - Increased aqueous humor absorption (decreased intraocular pressure).
Exocrine glands	<ul style="list-style-type: none"> • α_1 (and slight β_2): - increased secretions of salivary, lacrimal, and sweat glands. 	<ul style="list-style-type: none"> • M: decreased secretions.
Heart	<ul style="list-style-type: none"> • β_1 (and slight β_2, α_1, and DA_1): - Increased heart rate (positive chronotropic action). - Increased force of contraction (positive inotropic action). - Increased conduction velocity (positive dromotropic action). 	<ul style="list-style-type: none"> • M_2: - Decreased heart rate. - Decreased force of contraction. - Decreased conduction velocity.
Blood vessels (arteries and veins)	<ul style="list-style-type: none"> • α_1 (and may be α_2): -Vasoconstriction of coronary, pulmonary, renal, splanchnic, and skeletal muscle vessels (predominate). • β_1: Vasodilatation of coronary vessels. • β_2: Vasodilatation of skeletal muscle vessels. • DA_1: Vasodilatation of splanchnic and renal vessels. 	<ul style="list-style-type: none"> • M_3^a: Dilatation of blood vessels.
Lung	<ul style="list-style-type: none"> • α_1: - Bronchoconstriction. • β_2: - Bronchodilatation (predominant). - Decreased bronchial secretions. 	<ul style="list-style-type: none"> M_3: - Bronchoconstriction. - Increased bronchial secretion.
Pancreas	<ul style="list-style-type: none"> • α_1 (and may be α_2): - decreased insulin secretion. • β_2: Increased insulin and glucagon secretion (predominant). 	<ul style="list-style-type: none"> M: Increased insulin secretion.
Gastro-intestinal tract	<ul style="list-style-type: none"> • α_1 (and α_2): - Contraction of sphincters. - Decreased secretion. • β_2 (and α_1): - Decreased tone and motility. 	<ul style="list-style-type: none"> M: - Relaxation of sphincters. - Increased secretion. - Increased tone and motility. <p>These cause nausea, vomiting, and defecation</p>
Urinary bladder	<ul style="list-style-type: none"> • α_1: - Contraction of sphincters. • β_2: - Relaxation of detrusor wall muscle (decreased motility). 	<ul style="list-style-type: none"> M: - Relaxation of sphincters. - Contraction of detrusor wall muscle (increased motility). These cause urination.
Kidney	<ul style="list-style-type: none"> • β_1: - Increased renin secretion 	
Liver and metabolism	<ul style="list-style-type: none"> • α_1: - Increased gluconeogenesis. - Inhibition of Na^+-K^+ pump (increased s. K^+). • α_2: - Decreased lipolysis in liver and fat cells. - Increased glycogenolysis. • β_2: - Increased glycogenolysis. - Stimulation of Na^+-K^+ pump (decreased serum K^+). • β_3: - Increased lipolysis in liver and fat cells. 	<ul style="list-style-type: none"> M: - Increased glycogen synthesis.
Male sexual organs	<ul style="list-style-type: none"> • α_1: - Ejaculation. 	<ul style="list-style-type: none"> • M: - Erection.
Female sexual organs	<ul style="list-style-type: none"> • α_1: - Contraction of uterus (during pregnancy). • β_2: - Relaxation of uterus. 	<p><u>Nicotinic receptors:</u> (non-parasympathetic actions)</p> <ul style="list-style-type: none"> • Neuromuscular junction: contraction of skeletal muscles. • Autonomic ganglia: stimulation of sympathetic and parasympathetic systems. • Increased release of catecholamines from adrenal medulla and chromaffin cells. • Increased antidiuretic hormone release from the hypothalamus.
Others	<p><u>Platelets:</u></p> <ul style="list-style-type: none"> • α_2: - Increased platelet aggregation. • β_2: - Decreased platelet aggregation. <p><u>Muscles:</u></p> <ul style="list-style-type: none"> • α_1: - Contraction of piloerector muscles • β_2: - Tremors in skeletal muscles. <p><u>Allergic reactions:</u></p> <ul style="list-style-type: none"> • β_2: - Decreased histamine and leukotrienes release - Decrease mast cell aggregation. 	

Sympathomimetics

They are drugs that partially or totally mimic the actions of sympathetic nerve stimulation or adrenal medulla discharge.

Classifications

➤ **Catecholamines:** (they contain catechol nucleus). Most of them are directly acting drugs.

- 1- Endogenous: - Adrenaline.
- Noradrenaline.
- Dopamine (has direct and indirect action in high doses).
- 2- Synthetic: - Isoprenaline.
- Dobutamine.
- Dopexamine.
- Fenoldopam.
- Ibopamine.

➤ **Non-catecholamines:**

1- **Drugs acting via Adrenergic Receptors:**

• **Both directly and indirectly acting (dual):**

- Ephedrine.
- Metaraminol.

• **Indirectly acting** (they increase catecholamines by either increasing noradrenaline release or decreasing uptake): - Amphetamine.

• **Directly acting:** They act directly on the adrenergic receptors

- Selective α_1 agonists as phenylephrine and methoxamine.
- Selective β_1 and β_2 agonists.

All the above drugs (catecholamines and non-catecholamines) increase cAMP by activation of adenylate cyclase system.

2- **Drugs Acting via Non-adrenergic Mechanisms:**

- Drugs that acting on V_1 -receptors: Vasopressin.
- Drugs that decrease breakdown of cAMP: - Phosphodiesterase inhibitors
- Drugs increase intracellular calcium availability:
 - Digoxin.
 - Calcium salts.
 - Glucagon.
- Drugs that increase the response of contractile proteins to calcium: - Levosimendan.

Inotropes (Positive Inotropes):

They are drugs that affect myocardial contractility. They are mainly sympathomimetic drugs.

They are classified into:

➤ **Inoconstrictors:** inotropes that produce systemic vasoconstriction: as

- Noradrenaline.
- Adrenaline.
- Ephedrine.

➤ **Inodilators:** inotropes that produce systemic vasodilatation: as

- Dobutamine.
- Dopexamine.
- Isoprenaline (sometimes called isopreternol or isoproterenol).
- Phosphodiesterase inhibitors.

Dopamine is an inodilator at low dose, and an inoconstrictor at higher doses

Q: Discuss new aspects in inotropic drugs?

	Adrenaline (Epinephrine)	Noradrenaline (Norepinephrine)
Receptor activity	<ul style="list-style-type: none"> • β agonist: mainly (predominate). They are arranged according to potency as: <ul style="list-style-type: none"> - β_1: adrenaline = noradrenaline > isoprenaline > dopamine. - β_2: isoprenaline > adrenaline > noradrenaline > dopamine. • α agonist: adrenaline > noradrenaline > isoprenaline. 	<ul style="list-style-type: none"> • α agonist: mainly (predominate). Although it is less potent than adrenaline. • β agonist: both β_1 and β_2 As adrenaline.
Clinical effects It is mainly on the cardio-vascular system. The effects increase with increasing the doses.	<p><u>a- At low doses:</u></p> <ul style="list-style-type: none"> • β_1 effects: produce increased contractility and heart rate which in turn increase cardiac output and systolic blood pressure with increasing myocardial work (increased O_2 need and decreased O_2 supply). • β_2 effects: produce vasodilatation especially in skeletal muscles; therefore, no or slight decrease of diastolic blood pressure (although α receptors are stimulated, β_2 effects predominate). <p>Bronchodilatation occurs.</p> <p><u>b- At high doses:</u></p> <ul style="list-style-type: none"> • β_1 and β_2 effects: are as above. • α effects: produce potent vasoconstriction in renal and splanchnic blood vessels (decreasing their blood flow). This increases systolic blood pressure and may decrease cardiac output. Cerebral and coronary blood flow may be increased. <p>Inhibition of insulin release with hyperglycemia occurs.</p>	<p><u>At all doses:</u></p> <ul style="list-style-type: none"> • α effects: produce potent vasoconstriction resulting in an increase in blood pressure with a decrease in heart rate due to baroreceptor reflex. <p>Although β_2 receptors are stimulated, α effects predominate, resulting in vasoconstriction of skeletal blood vessels.</p> <ul style="list-style-type: none"> • β_1 effects: produce an increase in contractility. <p>Therefore, the net effect is:</p> <ul style="list-style-type: none"> - increased systolic and diastolic blood pressure. - bradycardia. - no change or decreased cardiac output. - increased myocardial work.
Side effects	<ol style="list-style-type: none"> 1- Arrhythmias especially ventricular types. 2- Hypertension, coronary ischemia, or cerebral hemorrhage. 3- Hyperglycemia. 	<ol style="list-style-type: none"> 1- Arrhythmias. 2- At high doses, it is a universal vasopressor leading to: ischemia and decreased renal blood flow. 3- Extravasation at the site of infusion leads to tissue necrosis
Uses and doses I.m. = intra-muscular I.v. = intravenous N.B.: All catecholamines are not taken orally because they are metabolized by MAO enzyme in the gut and liver.	<ol style="list-style-type: none"> 1- In acute anaphylactic shock: <ul style="list-style-type: none"> - I.m.: 0.5-1 mg (0.5-1.0 mL of a 1: 1000 solution). or - I.v.: 1 μg/kg (100 μg) increments up to 1 mg (1-10 mL of a 1: 10 000 solution). 2- In cardiac arrest: (due to α actions only, no role to β actions): <ul style="list-style-type: none"> - I.v. bolus: 1 mg push, repeated every 3 min. - Tracheal route: 2-3 mg, diluted to a volume of 10 mL. 3- In bronchial asthma: <ul style="list-style-type: none"> - Subcutaneous as a 0.1% solution. - Aerosol inhalation. 4- As an additive to local anesthetics to decrease the rate of absorption. This decreases the toxicity and increases the duration: <ul style="list-style-type: none"> - Without halothane: the maximum dose is 5 μg/kg of a 1: 100 000 solution. - With halothane: the maximum dose is 1 μg/kg of a 1: 200 000 solution. 10 mL over 10 min repeated with a maximum of 3 times/h. • In low cardiac output states and shock: <ul style="list-style-type: none"> - I.v. infusion: <ul style="list-style-type: none"> Low doses: 20-50 ng/kg/min up to 500 ng/kg/min. High doses: > 500 ng/kg/min up to 40 000 ng/kg/min. 6- Topical vasoconstrictor to aid hemostasis. 7- Test dose in epidural anesthesia to detect intravascular injection. 	<p><u>Uses:</u></p> <ol style="list-style-type: none"> 1- Septic shock (mainly) as there is low systemic vascular resistance. 2- Intraoperatively, after removal of pheochromocytoma. <p><u>Doses:</u> (Ampoule = 4 mg)</p> <ul style="list-style-type: none"> • I.v. infusion: via a central venous line: 20-200 ng/kg/min. <p>4 mg diluted in 500 mL D5W (8 μg/mL).</p> <ul style="list-style-type: none"> • I.v. bolus: 0.1 μg/kg.

Isoprenaline or Isopreternol (Isuprel)	Dopamine (Inotropin)	Dobutamine (Dobutrex)
<ul style="list-style-type: none"> • β agonist (both β_1 and β_2): only. There is no α action. Its structure is similar to epinephrine. 	<p>It is catecholamine precursor and neurotransmitter.</p> <ul style="list-style-type: none"> • At low doses: dopamine (DA_1 and DA_2) receptor agonist. • At moderate doses: DA_1, DA_2, β_1 and β_2 agonist. • At high doses: β_1 and α agonist and indirect action by releasing noradrenaline from adrenergic nerve terminals. 	<ul style="list-style-type: none"> • β agonist mainly. β_1: mainly β_2: less potent than isoprenaline. • α: very minimal action. There is no DA receptor action.
<p>At all doses:</p> <p>Similar to β_1 and β_2 effects of adrenaline</p> <ul style="list-style-type: none"> • β_1 effects: produce an increase in cardiac contractility and in heart rate. This, in turn, increases the cardiac output and systolic blood pressure. Myocardial work increases also. • β_2 effects: produce vasodilatation especially in skeletal muscles, renal and mesenteric vessels; therefore, no or slight decrease of diastolic blood pressure occurs. 	<p>At low doses:</p> <ul style="list-style-type: none"> • DA_1 effects: produce vasodilatation in renal and mesenteric vessels, resulting in increased renal and splanchnic blood flow. This increases glomerular filtration rate which leads to sodium and water excretion (i.e., diuretic and natriuretic actions). • Presynaptic DA_2 effects: <ul style="list-style-type: none"> - decrease intra-renal noradrenaline release resulting in vasodilatation. - Inhibit aldosterone secretion from the adrenal glands, resulting in decreased sodium reabsorption. Theoretically, it decreases renal O_2 consumption. <p>At moderate doses:</p> <ul style="list-style-type: none"> • DA_1 and DA_2 effects are still present. • β_1 and β_2 effects: as with adrenaline (see before). <p>At high doses:</p> <p>There are no DA actions.</p> <ul style="list-style-type: none"> • β_1 effects: as adrenaline. • α effects: produce potent vaso-constriction that decreases renal and splanchnic blood flow. • Indirect action: causes cardiac stimulation. 	<p>At all doses:</p> <ul style="list-style-type: none"> • β_1 effects: produce an increase in the cardiac contractility. This causes an increase in cardiac output and an initial increase in systolic blood pressure. The increase in heart rate is less than isoprenaline; therefore, it is used in coronary diseases and congestive heart failure. • β_2 effects: produce vasodilatation in skeletal muscles. This prevents the increase in blood pressure (or even decreases it). There is a diuretic and natriuretic action due to the improved cardiovascular action (but no direct action on renal vessels).
<p>1- Arrhythmias.</p> <p>2- Myocardial ischemia.</p> <p>3- Delayed gastric emptying that may interfere with enteral feeding and absorption in an intensive care patient</p>	<p>1, 2, and 3 as isoprenaline.</p> <p>4- Nausea and vomiting due to stimulation of chemoreceptor trigger zone (it is outside the blood brain barrier). Dopamine does not cross the blood brain barrier.</p> <p>5- Reduction of anterior pituitary hormones (prolactin, growth hormone, and TSH).</p> <p>6- Tissue necrosis if it is extravasated. It is treated by local infiltration of phentolamine.</p>	<p>Arrhythmias.</p>
<p>Uses:</p> <p>1- Heart block and atropine resistant bradycardia. It is used temporarily as a pharmacological pacemaker before insertion of a permanent one.</p> <p>2- Septicemia and cardiogenic shock.</p> <p>3- Severe asthma.</p> <p>Doses and routes:</p> <ul style="list-style-type: none"> • I.v. infusion: 10-400 ng/kg/min usually 4 mg diluted in 500 mL D5W (8 μg/mL). • Aerosol. 	<p>Uses:</p> <p>1- As a diuretic: clinical studies have not demonstrated any benefit of "low-dose" dopamine for renal protection or for the prevention and treatment of acute renal failure in critically ill patients. In fact, it induces regional redistribution of blood flow within the kidney by shunting blood away from the outer medulla to the cortex. This is potentially detrimental in acute renal failure given that the outer medulla is very susceptible to ischemic injury.</p> <p>2- Low cardiac output states as septic, cardiogenic, or hypovolemic shock. It may be used with vasodilators to decrease the afterload and improve cardiac output.</p> <p>Doses and routes:</p> <ul style="list-style-type: none"> • I.v. infusion via a central venous line. <p>Low-dose: 0.5-3 μg/kg/min Moderate-dose: 3-10 μg/kg/min High-dose: 10-20 μg/kg/min (5 mL ampoule contains 200 mg).</p>	<p>Uses:</p> <p>Low cardiac output states as</p> <ul style="list-style-type: none"> - septic shock (usually with noradrenaline). - Heart failure (usually with vasodilator drugs). <p>Doses and routes:</p> <p>I.v. infusion: 2.0-20 μg/kg/min (5 mL ampoule contains 250 mg)</p> <p>Either by:</p> <ul style="list-style-type: none"> - infusion pump: one ampoule diluted in 500 mL D5W (500 μg/mL). or - syringe pump: the same equations as dopamine.

Calculation of the Doses and the Infusion Rates:

For Adrenaline and Noradrenaline Administrations:

- By a syringe pump or micro-dripper (60 drops/mL):

Calculation of the amount of the drug "in milligrams" required to be diluted by D₅W up to 50 mL in a 50

mL-syringe is done as follows:
$$= \frac{\text{Body weight in kg} \times 3}{100}$$

Therefore, every 1 mL/h (or drop/minute) = 10 ng/kg/min

For example: if 80 ng/kg/min adrenaline is indicated in a 70 kg adult; so,

$$\frac{70 \times 3}{100} = 2.1 \text{ mg is required to be diluted by D}_5\text{W up to 50 mL in a 50 mL-syringe.}$$

Therefore, every 1 mL/h (or 1 drop/min) = 10 ng/kg/min.

As the patient needs 80 ng/kg/minute; so, 8 mL/h or 8 drop/min is given.

The presentation of adrenaline: a 1 mL-ampoule contains 0.25 mg or 1 mg.

The presentation of noradrenaline: a 4 mL-ampoule contains 4 mg or 8 mg.

For Dopamine, Dobutamine, Sodium Nitroprusside, or Nitroglycerin:

A) By a syringe pump, micro-dripper (60 drops/mL), or infusion pump:

At first, the rate of infusion in mL/h which corresponds to 1 µg/kg/minute is calculated as follows:

$$\frac{\text{Body weight in kg} \times 60}{\text{Formula concentration in } \mu\text{g/mL}}$$

For example:

- If 3 µg/kg/minute dobutamine is required in a 70 kg adult,

1 ampoule of dobutamine (250 mg) is diluted by D₅W up to 50 mL in a 50 mL-syringe (the formula concentration for this mixture is 250 mg/50 mL = 250 000 µg/50 mL = 5000 µg/mL),

$$\frac{70 \times 60}{5000} = 0.8 \text{ mL/h i.e., every 0.8 mL/h} = 1 \mu\text{g/kg/minute.}$$

As 3 µg/kg/minute is needed, the infusion rate of the syringe pump is adjusted as 3 × 0.8 = 2.4 mL/h.

- If 3 µg/kg/minute dobutamine is required in a 70 kg adult,

1 ampoule of dobutamine (250 mg) is diluted in 500 mL D₅W (the formula concentration for this mixture is 250 mg/500 mL = 250 000 µg/500 mL = 500 µg/mL),

$$\frac{70 \times 60}{500} = 8 \text{ mL/h i.e., every 8 mL/h} = 1 \mu\text{g/kg/minute.}$$

As 3 µg/kg/minute is needed, the infusion rate of the infusion pump is adjusted as 3 × 8 = 24 mL/h.

B) By a syringe pump or micro-dripper (60 drops/mL) as a single concentration:

Calculation of the amount of the drug "in milligrams" required to be diluted by D₅W up to 50 mL in a 50 mL-syringe is done as follows = body weight in kg × 3

Therefore, every 1 mL/h (or drop/minute) = 1 µg/kg/min

For example: if 5 µg/kg/min dopamine is indicated in a 70 kg adult; so,

$$70 \times 3 = 210 \text{ mg is required to be diluted by D}_5\text{W up to 50 mL in a 50 mL-syringe.}$$

Therefore, every 1 mL/h (or 1 drop/min) = 1 µg/kg/min.

As the patient needs 5 µg/kg/minute; so, 5 mL/h or 5 drop/min is given.

The presentation of dopamine: a 5 mL-ampoule contains 200 mg.

The presentation of dobutamine: a 5 mL-ampoule contains 250 mg.

The presentation of sodium nitroprusside: a 5 mL-ampoule contains 50 mg.

The presentation of nitroglycerin: a 5 mL-ampoule contains 50 mg or 50 mL-vial contains 50 mg.

Dopexamine

It is synthetic dopamine analogue.

Receptor Activity:

- β₂ agonist (> dopamine).
- DA₁ agonist (< dopamine).
- DA₂ agonist: weak action.
- Indirect action: It inhibits neuronal reuptake (uptake₁) of noradrenaline.

It has no direct actions on β₁ or α-receptors.

Clinical Effects:

- β_2 effects: - produce vasodilatation of skeletal muscle, splanchnic, and renal vessels, resulting in a decrease in blood pressure if the intravascular volume is not maintained.
- produce a mild increase in heart rate and contractility resulting in increased cardiac output (also due to the indirect action).
- DA_1 effects: cause diuretic and natriuretic action.

Side Effects:

1- Arrhythmias.

2- Nausea and vomiting due to stimulation of DA receptors in the chemoreceptor trigger zone.

Uses:

Low cardiac output states: as septic shock and heart failure to maintain splanchnic and renal blood flow.

Doses and Routes:

Iv. infusion: $0.5 \mu\text{g/kg/min}$ up to $6 \mu\text{g/kg/min}$ (diluted in D_5W).

Fenoldopam**Receptor Activity and Clinical Effects:**

- **Selective DA_1 agonist** (no α , β , or DA_2 actions): produces potent vasodilatation of:
 - renal vessels, resulting in diuresis and natriuresis.
 - systemic vessels, resulting in a decrease in blood pressure (with reflex tachycardia) within 15 minutes of infusion and a reduction of afterload which increases cardiac output.

There are no inotropic or venodilator actions. It has reno-protective action especially in high risk patients during vascular and cardiac surgeries.

Pharmacokinetics:

- It is metabolized only by conjugation in the liver to inactive metabolites.

Side Effects: due to the vasodilatation:

- Headache
- Flushing.
- Nausea.
- Hypotension and tachycardia.
- Increased intraocular pressure, so it is contraindicated in glaucoma.
- Allergic reactions up to anaphylactic shock due to its preservative sodium metabisulfite.

Uses:

- Acute and chronic renal failure.
- Perioperative hypertension and hypertensive emergencies; there is no rebound hypertension after its stoppage (unlike other vasodilator agents).
- Congestive heart failure.

Doses and Routes:

- Iv. infusion: $0.1 \mu\text{g/kg/min}$ increments up to $0.8 \mu\text{g/kg/min}$ until blood pressure is controlled.
- Oral route.

Ibopamine

It is a prodrug, which is converted to epinine (N-methyldopamine) after oral administration.

Receptor Activity and Clinical Effects:

- Nonselective DA receptors: It acts on both DA_1 and DA_2 . Its clinical effects are similar to dopamine.

Non-catecholamines**Ephedrine**

It is a naturally occurring sympathomimetic, but it is now produced synthetically.

Receptor Activity:

- Direct action on α and β (β_1 and β_2) receptors.
- Indirect action by a central stimulation, increasing noradrenaline release, and decreasing its reuptake.

Clinical Effects:

It is **similar to adrenaline** in cardiovascular and bronchial actions (see before) except that:

- it is **less potent**.
- and • it has a **10 times longer** duration of action ($t_{1/2} \beta = 3-6$ hours).
- **Tachyphylaxis** (a decreased response to repeated doses of the drug) occurs due to persistent occupation and down regulation of adrenergic receptors and depletion of noradrenaline stores.
- it **stimulates central nervous system** (it raises MAC of volatile anesthetics).
- It interacts with tricyclic antidepressant drugs and MAOIs especially in the first 14-21 days of treatment with these agents, resulting in a severe hypertensive response.

Uses:

1- **Treatment of hypotension** due to sympathetic blockade of **regional anesthesia** or general anesthesia **especially in obstetrics**, as it maintains uterine blood flow (due to its β_2 action) in contrast to pure α receptor vasoconstrictors that restore systemic blood pressure at the expense of uterine blood flow.

2- As a nasal decongestant.

Doses and Routes: (1-mL ampoule contains 25 or 50 mg)

- I.v. bolus: 5 mg increments (0.1 mg/kg for children), until hypotension is treated.
- Oral route: 25-50 mg, as its not metabolized by MAO in the gut.
- Nasal drops.

Phenylephrine**Receptor Activity:**

- Direct agonist action on α_1 and minimal agonist action on α_2 and β receptors in high doses.

Clinical Effects:

It is similar to **noradrenaline** in its cardiovascular actions (widespread vasoconstriction, more venous than arterial, with bradycardia) except that it is less potent and has a longer duration.

Uses and Doses:

- Nasal decongestant.
- Mydriatic agent in open angle glaucoma.
- Hypotensive states as during spinal anesthesia: i.v. bolus increments 0.5-1 $\mu\text{g/kg}$.
or i.v. infusion 0.5-1 $\mu\text{g/kg/min}$.

Vasopressin (Arginine-Vasopressin) (AVP)**(Previously Called Antidiuretic Hormone) (ADH)**

- It is a hormone synthesized in the hypothalamus, transported by nerve axons down to the posterior pituitary gland, and from there, secreted into the blood.
- The release of ADH is regulated by the osmolarity of the extracellular body fluids, changes in arterial pressure and intravascular volume, and the sympathetic nervous system.

Receptor Activity: It has an agonist action on:

- **V₁-receptors (vasomotor receptors):** it causes potent vasoconstriction and decreases splanchnic and renal blood flow; therefore, it is used in:
 - **refractory vasodilatory shock** e.g., septic shock, not responding to catecholamines, as an i.v. infusion 2-8 units/h.
 - Treatment of esophageal varices either as **localized infusion** (0.15-0.20 units/min) by selective arteriography or **i.v. infusion** (0.3-0.8 units/min). High doses as it causes congestive heart failure or heart ischemia (because it leads to coronary vasoconstriction).
 - **cardiopulmonary resuscitation** especially during prolonged resuscitation as an alternative to adrenaline (it is as effective as adrenaline or even more) as an i.v. bolus of 40 units once.
- **V₂-receptors (renal receptors):** it regulates water balance (the main action). It acts primarily on receptors in the distal convoluted tubules and collecting ducts of the nephron, to **increase free water reabsorption** and restore the plasma volume in response to hypotension.

Desmopressin (DDAVP; 1-desamino-8-D-arginine vasopressin)

It is a synthetic form of vasopressin that **does not cause vasoconstriction**. It is used in:

- 1- **Central diabetes insipidus:** Intranasal 5-10 μg /6-12 hours. It is long acting (12-24 hours). It can be used in outpatients and inpatients perioperatively.
- 2- **Hemophilia:** DDAVP increases factor VIII von Willebrand (VIII:vWF), factor VIII coagulant (VIII:C), and factor VIII-related antigen (VIIIr:Ag) activity by stimulating release from the endothelial cell storage sites. It is used in a dose of 0.3 $\mu\text{g/kg}$ 30 minutes before surgery. It is taken once.
- 3- **Thromboasthenia (platelet dysfunction):** e.g., during renal failure. DDAVP is used in the same dose as above. It is used to correct bleeding tendency before major surgery.

Disadvantages:

- It can not be repeated because such **stores become depleted** as factor VIII: C half life is only 12 hours.
- It also **releases tissue plasminogen activators (t-PA)**; therefore, DDAVP enhances fibrinolysis. The simultaneous use of an antifibrinolytic agent such as epsilon aminocaproic acid or tranexamic acid is recommended with it.
- Although vasopressin is a vasoconstrictor, **rapid injection of DDAVP may cause acute hypotension due to vasodilatation**.

Phosphodiesterase (PDE) III Inhibitors

Enoximone, Amrinone and Milrinone

The PDE III isoenzyme is present in the heart, blood vessels, and platelets.

Action:

They inhibit phosphodiesterase enzyme that breaks down cAMP, resulting in increased intracellular cAMP concentration which stimulates protein kinase C and leads to an increase in intracellular calcium.

Clinical Effects

- Increased cardiac contractility (positive inotropic action).
- Facilitation of diastolic relaxation (positive lusitropic action).
- Vasodilatation (systemic, coronary, and venous), resulting in decreased preload and afterload.
- Heart rate may increase or remain unchanged.

Therefore, unlike other sympathomimetics, they improve cardiac function without increasing oxygen demand.

Uses:

- 1- Chronic cardiac failure: especially if there is a decrease in the inotropic action of β -agonists (due to down regulation of β -receptors).
- 2- Acute refractory cardiac failure.

Glucagon

It is secreted by the α -cells of the pancreatic islets.

Action:

It increases adenylate cyclase activity via a membrane receptor and increases intracellular cAMP by a mechanism independent of the β -receptor. This leads to:

- Stimulation of hepatic gluconeogenesis (and as a part of stress response), resulting in hyperglycemia.
- Increased cardiac contractility i.e. a positive inotropic action.
- Nausea and vomiting.
- Hyperkalemia.

Uses:

- As inotropes only in **toxicity of β blockers or Ca^{++} channel blockers**.

Doses: 3-5 mg (0.03-0.05 mg/kg) i.v. bolus followed by 3-5 mg/h i.v. infusion

Levosimendan

It is the first drug in a new class of positive inotropic drugs called **calcium sensitizers**.

It is the levo-isomer of the racemic compound simendan, a pyridazinone-dinitrite derivative.

Action:

- It increases **calcium sensitivity (calcium sensitization)** in an **energy-independent** process and a **cAMP-independent** mechanism (unlike β agonists and PDE III inhibitors), **without increasing intracellular calcium**.

It binds to cardiac troponin C and stabilizes the conformational changes of troponin C, facilitating actin-myosin cross-bridge formation.

- At higher concentration, it selectively inhibits PDE-III isoenzyme, augmenting the inotropic action.

Clinical Effects:

- **Positive inotropic action:**

- It increases contractility without an increase in oxygen consumption or tendency to dysrhythmias as these side effects are related to the increased intracellular calcium such as with β -agonists (epinephrine, norepinephrine, and dopamine) and PDE-III inhibitors (amrinone and milrinone), but levosimendan acts by increasing calcium sensitivity.

- It does not impair relaxation during diastole because its activity is related to calcium concentration; therefore, during systole, calcium concentrations are high and, as a result, levosimendan is more active. Conversely, during diastole, calcium concentrations are lower and levosimendan is inactive.

- **Vasodilatation:** by opening K^+ channels via a ATP-dependent mechanism.

It produces systemic, pulmonary, and coronary vasodilatation and increases coronary blood flow.

Uses:

- Acute heart failure: it is superior to dobutamine.

Doses: I.v. bolus: 12 $\mu\text{g/kg}$ followed by 0.1-0.2 $\mu\text{g/kg/min}$.

Selective β_2 Agonists

Agents:

- Salbutamol (*Ventolin*) (duration 3-5 hours)
- Terbutaline (*Bricanyl*) (duration 3-5 hours).
- Ritodrine. (*Yutopar*)
- Albuterol.
- Formoterol (*Berotec*) (long acting).
- Salmeterol (long acting).

Receptor Activity:

- At low doses: they are selective β_2 agonists (increasing intracellular cAMP).
- They are - partial agonist (i.e., their maximal effect at β_2 -receptors is less than that of isoprenaline).
 - partially selective (i.e., their selectivity is lost at high doses).

Clinical Effects and Uses:

• Bronchodilatation:

They also - inhibit mast cell mediator release.

- inhibit plasma exudation and micro-vascular leakage.
- prevent airway edema.
- increase mucus secretion.
- increase mucociliary function.

Therefore, they are used in the treatment of **bronchial asthma**, chronic obstructive airway disease, hyperactive airway, and bronchospasm due to anaphylaxis, aspiration, or inhalation of toxins.

They have little effects on the heart. For example, salbutamol which can be given as:

- Inhalational as a metered dose aerosol inhaler (1-2 puffs, each 100 μ g) or nebulizer (2.5-5 mg).
- I.v. bolus (250 μ g) or infusion (5 μ g/min)
- Oral (2 mg tablets/6 hours).

• **Peripheral vasodilatation:** therefore, they are used in the treatment of **peripheral vascular diseases**.

• **Relaxation of the uterus:** therefore, they are used as **tocolytics in the treatment of premature labor**, for example, ritodrine orally or as infusion.

Side Effects:

- Due to other β_2 actions:
 - Increased intraocular pressure.
 - Hypokalemia due to stimulation of sodium-potassium pump.
 - Decreased gastrointestinal tone and motility, leading to constipation.
 - Skeletal muscle tremors and weakness.
 - Hyperglycemia; which if occurs in a mother, reactive fetal hypoglycemia results.
- Due to β_1 actions (at high doses): - Tachycardia and arrhythmias.
- Due to chronic and prolonged usage: - Tachyphylaxis and tolerance. They occur due to down regulation of the receptors.

Sympatholytics

A) Centrally Acting Drugs:

They block central sympathetic outflow. They are mainly α_2 agonists. They include:

- | | | |
|--------------------------------|---------------|----------------------------------|
| • α methyl dopa. | • Clonidine. | • Dexmedetomidine. |
| • Azepevole. | • Moxonidine. | • Guanabenz (<i>Wyntensin</i>) |
| • Guanfacine (<i>Trenex</i>) | | |

1- α Methyl dopa: (*Aldomet* or *Adamat*)

It is an analogue of levodopa.

Action:

- It is a **prodrug** which crosses the blood brain barrier and is converted in central neurons to **α -methyl noradrenaline** and **α -methyl adrenaline**. The latter **stimulates central presynaptic α_2 receptors** (i.e., it acts as a **false transmitter**). It has an α_2 : α_1 selectivity ratio of 10: 1.

This leads to **decreased central sympathetic outflow**, resulting in peripheral vasodilatation and reduction of systemic vascular resistance, but both cardiac output and renal blood flow are maintained.

Uses:

It is restricted to **pregnancy-associated hypertension** because it does not affect the fetus although it crosses the placenta.

Therefore, it is used as an antihypertensive agent.

Side Effects:

- Due to reduction of sympathetic actions:
 - Dry mouth.
 - Nasal congestion.
 - Bradycardia and orthostatic hypotension.
 - Sedation and galactorrhea.
 - Nausea and diarrhea.
- Due to idiosyncratic reactions:
 - Positive Coombs' test (difficulty in blood cross-matching).
 - Hemolytic anemia, thrombocytopenia, and leucopenia.
 - Hepatitis.
 - Drug fever.
 - Lupus-like syndrome.

Doses:

- Oral: 125-250 mg/12 hours.
- I.v. infusion: 250-1000 mg/6 hours.

2- Clonidine: (Catapres)

It is an imidazoline compound.

Action:

It is a selective partial agonist for α_{2B} (no effect on α_{2A} or α_{2C}) with an $\alpha_2 : \alpha_1$ ratio of 200: 1.

It also acts on imidazoline (I) receptors which control arterial blood pressure.

- It stimulates **central presynaptic α_2 receptors** (in the hypothalamus and locus caeruleus): resulting in decreased noradrenaline release (i.e., decreased central sympathetic outflow) which in turn leads to hypotension, bradycardia, sedation, and anxiolysis.
- It stimulates **central postsynaptic α_2 receptors** and **imidazoline (I) receptors** (in the medulla): resulting in decreased blood pressure, heart rate, and myocardial contractility. This causes reduction of myocardial O_2 requirements.
- It stimulates **peripheral presynaptic α_2 receptors**: resulting in decreased noradrenaline release.
- It stimulates **peripheral postsynaptic α_1 and α_2 receptors** (in overdosage and after rapid i.v. injection): resulting in transient elevation of blood pressure.
- It stimulates **central postsynaptic α_1 receptors** (only in very high doses), resulting in limitation of its anesthetic action.
- It **decreases noradrenaline synthesis** by inhibition of dopamine β -hydroxylase enzyme and N-methyltransferase enzyme.
- It **decreases renin activity** and renal vascular resistance; therefore, it maintains renal blood flow.
- It has an **analgesic action** via action on pre- and postsynaptic α_2 receptors (that is not reversed by naloxone) due to:
 - stimulation of descending inhibitory pathways from the locus caeruleus,
 - inhibition of nociceptive transmission (and inhibition of release of substance P) at the spinal cord,
 - potentiation of the action of opioids and local anesthetics.

Uses:

- Moderate and severe hypertension especially in patients with high plasma renin.
- During management of opioid, benzodiazepine, nicotine (tobacco) and alcohol withdrawal symptoms as it decreases signs of sympathetic overactivity.
- As a preanesthetic medication: because it controls blood pressure, attenuates the stress response, produces sedation, acts as an antisialagogue, and potentiates other i.v. and inhalational anesthetics (up to 50%), but within limits (due to its α_1 action in high doses).
- With regional anesthesia, because it speeds the onset and prolongs the duration of the block.
- Clonidine suppression test to differentiate patients with essential hypertension from those with suspected pheochromocytoma as acute administration of clonidine decreases the plasma noradrenaline levels in essential hypertension, but not in pheochromocytoma.
- Postoperative shivering and opioid-induced muscle rigidity, as it decreases them.

- Diarrhea of autonomic neuropathy.
- Chronic pain e.g., diabetic neuropathy and migraine.
- Menopausal hot flushes.

Side Effects:

- Due to decreased sympathetic activity; as α -methyl dopa (see above).
- Due to sudden clonidine cessation (after 1 month usage), acute withdrawal syndrome occurs with hypertensive crisis, agitation, and sympathetic overactivity due to up-regulation of the receptors, which is treated by reinstitution of clonidine therapy or giving α and β blockers.

Drug Interactions:

- With tricyclic antidepressants, hypertension may occur (due to their α -blocking action).
- With central nervous system depressants, excessive drowsiness occurs.

Pharmacokinetics:

It is lipid soluble and crosses the blood brain barrier and the placenta. Its elimination $t_{1/2}$ is 9-12 hours. 50% of clonidine is metabolized in the liver into inactive metabolites and 50% is excreted unchanged by the kidney.

Doses:

- Oral: 200-300 μg (3-5 $\mu\text{g}/\text{kg}$) for **premedication** (1 hour preoperatively) **and as an antihypertensive** (every 12 hours).
- Epidural: 1-2 $\mu\text{g}/\text{kg}$ for **analgesia and potentiation of other local anesthetics**.
- I.v.: 200-300 μg (3-5 $\mu\text{g}/\text{kg}$) for **anesthesia (and decreasing the stress response)**.
- Transdermal patch: 0.1 or 0.2 mg released/day. The patch is exchanged every 7 days **for chronic pain and menopausal hot flushes**.

It can be given also by the i.m. (2 $\mu\text{g}/\text{kg}$), intrathecal (75-150 μg), sublingual and rectal routes.

3- Dexmedetomidine: (*Precedex*)

Action: It is similar to clonidine, with the following differences:

- It is a selective full agonist on α_{2B} and partial agonist on α_{2A} and α_{2C} . The $\alpha_2: \alpha_1$ selectivity ratio is 1600: 1 (it has no action on α_1 receptors; therefore, it potentiates the MAC of inhalational anesthetics up to 90%). It is more selective and effective on α_2 receptors than clonidine
- It has a **shorter duration**; its elimination $t_{1/2}$ is 2 hours only and it is metabolized in the liver to metabolites which are excreted in the urine.

Clinical Uses:

It is mainly used for intraoperative sedation e.g., during regional anesthesia or awake fiberoptic intubation, and for short-term **sedation in the intensive care units** especially during mechanical ventilation with the following advantages:

- Although patients are sedated, they can be **easily aroused**.
- It **blocks sympathetic system with reduction of tachycardia and hypertension** which occur during mechanical ventilation.
- It **does not cause respiratory depression**; therefore, there is no need to stop it before extubation, unlike propofol, benzodiazepines, and opioids.

Side Effects:

As clonidine (see above).

Acute withdrawal syndrome occurs after only 48 hours usage due to its increased affinity to receptors in comparison with clonidine.

Doses:

- I.v.: loading 1 $\mu\text{g}/\text{kg}$ slowly over 10 min then a maintenance dose of 0.2-0.7 $\mu\text{g}/\text{kg}/\text{h}$.

4- Azepevole

It is similar to dexmedetomidine as it is a selective α_2 -receptor agonist.

5- Moxonidine (*Cynt*)

Action:

- It acts **mainly on imidazoline (I) receptors** that are present in the medulla, resulting in an antihypertensive action with much less sedative action than clonidine.
- It has a minimal effect on α_2 -receptors.

B) Peripherally Acting Drugs:

They block autonomic ganglia, peripheral adrenergic neurons, or postsynaptic adrenergic receptors.

1) Ganglion Blocking Drugs:

They include: hexamethonium, trimetaphan (trimethaphan or *Arfonad*), and pentolinium.

Action:

They produce competitive inhibition of nicotinic receptors at the autonomic ganglia; both sympathetic and parasympathetic ganglia, preventing the effect of ACh at the receptors.

Clinical Effects:

- Blockade of sympathetic ganglia produces vasodilatation and decreased myocardial contractility, resulting in hypotension.
- Blockade of parasympathetic ganglia produces mydriasis, increased heart rate, dryness of secretions, and decreased gastrointestinal motility with constipation and retention of urine.

2) Adrenergic Neuron Blocking Drugs:

Guanethidine:

Action:

- It decreases sympathetic activity by **interfering with the storage of noradrenaline** in the storage vesicles as it competitively binds to noradrenaline binding sites in storage vesicles and prevents uptake of noradrenaline inside the vesicles, resulting in metabolism of noradrenaline in the cytoplasm by MAO enzyme.

Uses: It is rarely used nowadays as an antihypertensive agent but it is still used in:

- Intravenous regional sympathetic blockade in treatment of chronic limb pain associated with reflex sympathetic dystrophy or complex regional pain syndromes.

Bretylum:

It is similar to guanethidine in action. It also has a class III antiarrhythmic action.

It is used mainly in treatment of resistant ventricular tachyarrhythmias.

Reserpine: (In *Brinerdin* with clopamide "a thiazide diuretic" and dihydroergocristine)

It is similar to guanethidine. It is rarely used nowadays.

3) α -Adrenergic Receptor Antagonists (α -Blockers)

a) Nonselective α -Antagonists

They include: - **Phentolamine** (*Regitine*, *Rogetine*, or *Rogitamine*): (it reversibly inhibits the receptor) i.v. 2-5 mg increments or i.v. infusion.

- **Tolazoline.**

b) Selective α_1 -Antagonists

They include: - **Phenoxybenzamine** (*Dibenzyline*) (it binds covalently, irreversibly, and non-competitively to the receptors resulting in prolonged duration of action up to several days till regeneration of the receptors occurs). It also has some α_2 antagonist action.

- **Prazosin** (*Minipress*), **doxazosin** (*Cardura*), **terazosin** (*Hytrin*), **indoramin**, and **urapidil**.

c) Selective α_2 -Antagonists

They include **yohimbine**. They are not used nowadays due to their side effects.

N.B.: Other agents with α -blocking action:

- Ergot alkaloids as ergotamine and methergine.
- Chlorpromazine.
- Droperidol.

Action, Uses, and Side Effects: (due to sympathetic blocking action)

- They produce **vasodilatation**, both arterial and venous, resulting in decreasing the afterload and preload. This augments the cardiac output; therefore, they are used as
 - the second line of treatment in hypertension, but postural hypotension and reflex tachycardia are common due to blockade of presynaptic α_2 -receptors especially with the nonselective agents and yohimbine. These side effects are less with the selective α_1 -agents.
 - preoperative management of pheochromocytoma especially phenoxybenzamine.
 - treatment for hypertensive crisis.
 - treatment for peripheral vascular diseases.

N.B.: Extravasation of noradrenaline causes local tissue necrosis.

- **Relaxation of the urinary bladder;** therefore, they are used in benign prostatic hyperplasia.
- Relaxation of the dilator muscle of the eye, resulting in **miosis**.
- Relaxation of the gastrointestinal tract, resulting in **diarrhea**.
- Decreased secretion of salivary glands (**dry mouth**) and lacrimal glands (**dry eyes**).
- **Impaired ejaculation.**

4) β -Adrenergic Receptor Antagonists (β -Blockers)

They are structurally similar to β -agonists e.g., isoprenaline, but they do not activate adenylate cyclase enzyme.

Agents:

	Relative β_1 cardio-selectivity	Intrinsic sympathetic activity	Membrane stabilizing activity	Vasodilatory action	Elimination	Lipid solubility	Active metabolites
Acebutolol (<i>Sectral</i>)	\pm	+	+	-	Hepatic, renal	Medium	Yes
Atenolol (<i>Tenormin</i> , <i>Atelol</i> , or <i>Bolkium</i> with chloro-thalidone)	+	-	-	-	Renal	Low	No
Bisoprolol (<i>Bisocard</i> , <i>Zebeta</i> , <i>Concor</i> , or <i>Concor-5 plus</i> with hydrochloro-thiazide)	++	-	-	-	Hepatic, renal	Low	No
Carvedilol (<i>Carvedilol</i> , <i>Cardiolol</i> , <i>Dilatrend</i> , <i>Dilatrol</i> , or <i>Carvid</i>)	-	-	?	+	Hepatic	High	Yes
Celiprolol	+	+	?	+		Low	
Esmolol	-	-	-	-	Plasma hydrolysis	High	No
Labetalol	-	\pm	+	+	Hepatic	High	No
Metoprolol (<i>Betaloc</i> , <i>Lopressor</i> or <i>Low press</i>)	+	-	\pm	-	Hepatic	High	No
Nadolol (<i>Corgard</i>)	-	-	-	-	Renal	Low	No
Oxprenolol	-	+	+	-	Hepatic	High	No
Pindolol (<i>Viskin</i>)	-	++	\pm	-	Hepatic	Medium	No
Propranolol (<i>Inderal</i>)	-	-	++	-	Hepatic	High	Yes
Sotalol (<i>Betacor</i>)	-	+	+	-	Renal	Low	No
Timolol (<i>Blocadren</i>)	-	+	\pm	-	Hepatic, renal	High	No

• β_1 -cardioselectivity:

These agents lack side effects of β_2 blockade as bronchospasm, hypoglycemia, or intermittent claudications. It is relative as it is lost in all agents at high doses.

• Intrinsic Sympathetic Activity or Partial Agonist Activity:

In patients with low level of sympathetic discharge e.g., at rest, these drugs have a stimulant effect on the heart.

In patients with high level of sympathetic discharge e.g., during exercise, these drugs purely act as blockers.

• Membrane Stabilizing Activity (Quinidine-Like Actions, or Local Anesthetic Activity):

These agents decrease excitability and automaticity of the heart. This effect occurs at drug concentrations higher than those used therapeutically; therefore, it has of a little clinical significance.

- **Vasodilatory Action:**

These agents either have: - a β_2 -partial agonist action as celiprolol or
- an additional vasodilatory action as carvedilol.

- **Lipid Solubility:**

Agents with high lipid solubility have extensive 1st pass hepatic metabolism, resulting in low bioavailability with short half-lives necessitating frequent dosing. These agents can cross the blood brain barrier producing central nervous side effects and can be used in renal failure, while agents with low lipid solubility need less frequent dosing, produce less central nervous system side effects and cannot be used in renal failure.

Actions and Uses:

1- Antiarrhythmic Actions:

- Especially in - supraventricular arrhythmias, atrial flutter and fibrillation.
- digitalis-induced arrhythmias.
- Mechanisms: - They decrease the rate of discharge from the sino-atrial (SA) node and other ectopic foci.
- They decrease conduction of atrio-ventricular (AV) node and other anomalous pathways of the heart.
- Sotalol has both class-II and class-III antiarrhythmic action.

2- Antianginal Actions:

- Especially in - exertional angina pectoris (coronary atherosclerosis). They may worsen variant or Prinzmetal's angina due to coronary spasm.
- prophylaxis to avoid myocardial infarction.
- Mechanisms: - The negative chronotropic effect decreases cardiac work and myocardial O₂ consumption and increases diastolic time filling supplying more O₂ to the heart.
- The negative inotropic effect decreases myocardial contractility and O₂ need.
- They shift subepicardial flow to subendocardial flow supplying more O₂.
- They inhibit platelet aggregation.
- During exercise, all β blockers limit the increase in heart rate which is beneficial, while during rest, β blockers without intrinsic sympathetic activity are more effective on the heart rate and as antianginal therapy than other agents with intrinsic sympathetic activity.

3- Antihypertensive Actions:

- They are considered the first-line therapy for treatment of hypertension. They can be used alone or with other drugs as diuretics.

They are used as adjuvants to direct vasodilators to prevent reflex tachycardia in hypotensive anesthesia. They prevent the pressor response to intubation and emergence (tachycardia and hypertension).

- Mechanisms: The exact mechanism is unknown.

1- They **produce negative inotropic and chronotropic effects** that decrease cardiac output and in turn blood pressure, but after long term therapy, the cardiac output tends to return to the pretreatment value although the blood pressure is still decreased.

2- They **decrease central sympathetic outflow** by acting on the hypothalamus, but different drugs vary widely in their lipophilic properties and in crossing the blood brain barrier although they have similar effects on blood pressure.

3- They **decrease renin secretion** from the kidneys. Nonselective agents as propranolol and timolol are more effective in decreasing renin secretion than the cardio-selective agents, but all agents have similar effects on blood pressure. Actually, there is no relation between low rennin levels and the reduction of blood pressure.

4- They **decrease peripheral vascular resistance** due to altering prostaglandins in the vessels, but β blockers may increase peripheral vascular resistance due to unopposed α -action. This effect is less with cardio-selective agents.

5- They **may inhibit noradrenaline release** by blocking the presynaptic β_2 receptors.

6- They **may reset the baroreceptors** to control blood pressure at a lower level.

- Actually, several mechanisms are involved in controlling blood pressure; this is evidenced by:

- The hypotensive effect begins within an hour of administration of β blockers, but the full hypotensive effect (i.e., plateau effect) occurs only after 2 weeks from the start of treatment.
- During chronic administration, the hypotensive effect of β blockers lasts longer than the pharmacological half-life; therefore, a single daily dose is therapeutically adequate.
- Regardless of the pharmacological profile, all β blockers are equally effective as hypotensive

agents at rest and during exercise; therefore, patients unresponsive to one β blocker are generally unresponsive to all.

N.B.: In antianginal action, there is more direct relationship between the plasma concentration of β blockers and their antianginal effect; therefore, β blocker's plasma concentration must be maintained throughout the 24 hours to achieve this in a single daily dose; so, long acting drugs as atenolol or nadolol and slow release preparations as propranolol-LA are more effective.

4- In Treatment of Congestive Heart Failure:

- Especially bisoprolol, metoprolol, and carvedilol improve ventricular function. They must be introduced cautiously in heart failure as symptoms may initially worsen, and ventricular function improves only after 1 month of therapy.
- Mechanism: - They produce up-regulation of β -receptors which are already down-regulated due to prolonged sympathetic and catecholamine stimulation that occurs in heart failure. The down-regulation of the receptors impairs the ventricular function and produces ventricular remodelling while the up-regulated receptors improve the ventricular function.
- They also decrease the heart rate and produce antiarrhythmic action.

5- Other Actions and Uses:

- 1- **Hypertrophic obstructive cardiomyopathy** because β blockers decrease left ventricular contraction and emptying which in turn decreases the outflow obstruction.
- 2- **Acute dissecting aortic aneurysm** because β blockers decrease the force of myocardial contractions.
- 3- **Gastrointestinal bleeding** in hepatic cirrhosis because β blockers decrease portal hypertension due to splanchnic vasoconstriction.
- 4- **Thyrotoxicosis** because β blockers decrease the increased sympathetic symptoms as elevated heart rate and tremors and they prevent peripheral conversion of T_4 to T_3 .
- 5- **Pheochromocytoma**, but they should be preceded by α -blockers.
- 6- **Open angle glaucoma** because they decrease aqueous humor formation.
- 7- **Migraine prophylaxis.**

Side Effects:

A) Due to β -Blocking Actions:

- 1- β_1 -blockage causes: - heart failure especially in patients with poor left ventricular function,
 - bradycardia and atrio-ventricular block,
 - hypotension
- 2- β_2 -blockage causes: - bronchospasm especially the non-selective agents,
 - masking of the symptoms of hypoglycemia such as tachycardia and sweating,
 - peripheral vasoconstriction resulting in peripheral ischemia, Raynaud's phenomenon, intermittent claudication, cold extremities, and muscle fatigue during exercise, by the nonselective agents due to the unopposed α vasoconstrictive action,
 - decreased blood flow to the liver and kidneys, resulting in reduction of drug metabolism and excretion,
 and - hyperkalemia especially in diabetic or uremic patients.

B) Due to Idiosyncratic Reactions:

- 1- Central nervous system: **nightmares, vivid dreams, hallucinations, and mental depression** especially in elderly patients treated with lipophilic drugs.
- 2- **Nausea, vomiting, and diarrhea or constipation.**
- 3- **Increased plasma triglycerides** and decreased high density lipoprotein- cholesterol (HDL-cholesterol).
- 4- **Allergic reactions as rash and fever.**

C) Abrupt Withdrawal of β -Blockers for 24-48 hours after chronic usage results in arrhythmias, angina, and rebound hypertension due to upregulation of the receptors where the normal circulating catecholamines act on the up-regulated receptors. This is very dangerous in ischemic heart patients on β blockers.

Treatment of β -Blocker Toxicity:

- 1- Atropine, isoprenaline, dobutamine, or temporary pacemaker (for the negative chronotropic effects).
- 2- Calcium chloride i.v. 5-10 mg/kg.
- 3- Glucagon infusion (for the negative inotropic effects).

Drug Interactions:

1) Pharmacokinetic Interactions:

- Drugs that induce or inhibit hepatic metabolism affect the metabolism of lipophilic β blockers.
- Drugs that decrease hepatic blood flow as cimetidine or β -blockers decrease the metabolism of other lipophilic β -blockers, lignocaine and other amide local anesthetics, or chlorpromazine.

2) Pharmacodynamic Interactions:

- Potentiation: β blockers potentiate the action of the following drugs:
 - The vasopressor effect of sympathomimetics (with α and β actions), leaving unopposed α action.
 - The vasopressor effect of abrupt clonidine withdrawal.
 - The antihypertensive effect of other nonselective or vasodilator β -blockers.
 - The hypoglycemic effect of insulin and oral hypoglycemic drugs.
 - The bradycardia and heart block of calcium channel blockers.
- Antagonism: Non-steroidal anti-inflammatory drugs antagonize the antihypertensive effect of β -blockers due to inhibition of formation of vasodilator prostaglandins.

Individual β -Blockers

Propranolol

It is a nonselective β -blocker, similar to other agents except:

- It is a long acting β -blocker with elimination half-life 100 min.
- Doses:
 - I.v. (1 mL-ampoule contains 1 mg): 0.5 mg increments every 3-5 min until the response is reached. Total doses rarely exceed 0.15 mg/kg.
 - Oral tablets 20 and 40 mg/8 hours.
- In thyrotoxicosis: 160-480 mg/day tablets (40-120 mg/6 hours) for 2 weeks preoperatively and continued for 7-10 days postoperatively (it is given every 6 hours due to the increased metabolism in thyrotoxicosis).

Esmolol

It is similar to other β -blockers except:

- It is an **ultra-short β -blocker** with a duration of 10-20 min due to:
 - Its rapid redistribution ($t_{1/2\alpha} = 2$ min)
 - Its rapid hydrolysis by red blood cell esterase ($t_{1/2\beta} = 9$ min) (not by plasma cholinesterase).

It has the same side effects as other β -blockers, but it can be reversed within minutes after cessation of the drug administration.

- It is mainly used to prevent the pressor response to intubation, treat intraoperative tachycardia or hypertension, and treat supraventricular arrhythmias e.g., atrial flutter or fibrillation.
- Doses:
 - I.v. bolus (e.g., before intubation): 0.2-0.5 mg/kg up to 2 mg/kg over 1 minute.
 - I.v. infusion (for longer term therapy): loading by i.v. bolus then infusion 50 μ g/kg/min. The dose is increased incrementally every 5 minutes to a maximum 500 μ g/kg/min.

5) Mixed Antagonists

Labetalol (Trandate, or Normodyne)

Action:

- It is a competitive α_1 -, β_1 - and β_2 -antagonist. It is more active at β - than at α -receptors in an α_1 : β action ratio of 1: 3 (after oral intake) or 1: 7 (after i.v. intake).
- At low doses (5-10 mg i.v.): it decreases blood pressure without tachycardia.
- At higher doses: β -action becomes more prominent, with negative inotropic and chronotropic effects.
- It has intrinsic β_2 -agonistic activity leading to vasodilatation.
- In large doses, it has membrane stabilizing activity.
- It also prevents neuronal uptake of noradrenaline.

Clinical Effects and Uses:

- α_1 blocking causes vasodilatation which leads to hypotension.
- β blocking prevents reflex tachycardia.

Therefore, it is used in - preoperative treatment of pheochromocytoma

- controlling hypertensive crisis e.g., abrupt withdrawal of clonidine or β -blockers
- pregnancy associated hypertension
- hypotensive anesthesia.

Pharmacokinetics: It is mainly metabolized by the liver.

Doses:

- I.v. bolus: 0.1-0.25 mg/kg increments, over 2 minutes. It can be repeated twice every 10 minutes.
- I.v. infusion: 2 mg/min (200 mg diluted in 250 mL D₅W). The dose can be increased every 30 minutes until the response is reached.
- Oral tablets: 100 mg/12 hours.

Carvedilol (*Cardiolol cs, Dilatrend, Dilatrol, Carvid, Coreg or Carvipress*)

It is similar to other β -blockers except:

- It has the following actions:
 - an antagonist action at α_1 - and β -receptors with relative β : α_1 selectivity of 10: 1 and no partial agonist activity.
 - antioxidant activity.
 - inhibition of endothelin synthesis.
 - calcium channel blocking action in high doses.
- It is mainly used in congestive heart failure.

N.B.: I_F Channel Blockers

They are a recent group of cardiovascular drugs, example: Ivalrudine.

- They control heart rate and decrease angina.
- I_F channels control the inward Na/K depolarizing current in phase IV diastolic depolarization in pacemaker cells, especially in the SA node.

Para-symphathomimetics (Parasympathetic Agonists)

Most para-symphathomimetic drugs are not used nowadays.

Anticholinesterases (Cholinesterase inhibitors) are indirect acting para-symphathomimetics and have been discussed before in the chapter of "Pharmacology of anesthesia and intensive care".

Para-symphatholytics (Anticholinergics) (Chronotropes) (Anti-muscarinics) (Para-symphathetic Antagonists)

The most commonly used in anesthetic practice are - Atropine.

- Scopolamine (Hyoscine).
- Glycopyrrrolate (Glycopyrronium bromide).

Atropine**Mechanism of Action:**

They block acetylcholine (ACh) muscarinic receptors by competitive inhibition with ACh.

Pharmacological Action and Side Effects:

These actions can be estimated from the actions of the parasympathetic system, as they produce the reverse of these actions due to unopposed sympathetic actions.

1- Eye:

- **Mydriasis**, resulting in blurred vision and photophobia.
 - **Cycloplegia** due to paralysis of ciliary muscles, leading to inability to accommodate for near vision.
- Both actions precipitate acute attacks of glaucoma in patients with a narrow anterior chamber.

2- Exocrine Gland Secretion: (all glands are affected except breast milk glands)

- **Decreased secretion** of - lacrimal glands, resulting in dry and sandy eyes
 - salivary glands, resulting in dry mouth (i.e., antisialagogue)
 - bronchial glands, resulting in viscid sputum
 - sweat glands, resulting in dry skin (and atropine fever especially in infants and children)
 - gastric acid, and gastric mucous cells, resulting in a little change in gastric acid pH.

3- Heart:

- **Initial bradycardia** due to - blockade of presynaptic muscarinic receptors which increase ACh release. and due to - central effects.

• **Tachycardia** due to blockade of M_2 receptors on the SA node. It occurs more commonly in young patients and athletes who have higher vagal tone than elderly patients and infants. It is harmful in patients with ischemic heart diseases.

4- Blood Vessels:

• At **therapeutic doses**, there is a **little effect** on the peripheral vasculature due to the paucity of direct cholinergic innervations despite of the presence of cholinergic receptors.

• At **larger doses**, **vasodilatation** of cutaneous blood vessels occurs, resulting in **atropine flush** due to a direct action because atropine prevents calcium passage via the blood vessel wall.

5- Lung:

• **Bronchodilatation.**

• **Decreased viscid bronchial secretions.**

6- Gastrointestinal Tract:

• **Decreased motility**, resulting in prolongation of gastric emptying time that increases the **risk of aspiration.**

• **Decreased lower esophageal sphincter pressure.**

• **Decreased gastric secretions.**

7- Urinary Bladder:

• **Decreased motility**, resulting in **urine retention** especially in elderly patients with prostatic hypertrophy.

8- Central Nervous System:

• Initially, **central nervous system stimulation** occurs, resulting in excitation, restlessness, hallucinations, and convulsions. This is followed by cerebral depression, leading to sedation, and amnesia up to coma.

• It can be used in treatment of - Parkinsonism (it decreases tremors and rigidity).

- Motion sickness.

Atropine (and Other Anti-Muscarinic Drugs) Poisoning

Causes: Overdosage of either:

• **Quaternary amine drugs (such as glycopyrrolate):** they produce **excessive peripheral actions as atropine** without central nervous system actions because they do not cross the blood brain barrier, in addition to **postural hypotension** which occurs due to autonomic ganglion blockade.

• **Tertiary amine drugs (such as atropine and scopolamine):** they produce **excessive peripheral and central actions as atropine** because they cross the blood brain barrier. This is called **central anticholinergic syndrome.**

Precipitating Factors:

• Concomitant use of drugs having anticholinergic actions such as tricyclic antidepressants, antihistaminics, and antipsychotic drugs.

Clinical Pictures:

The symptoms appear quickly and may persist for some days.

The patient is described as - hot as a hare (atropine fever),

- blind as a bat (blurred vision),

- dry as a bone (decreased sweating and dry skin "xerostomia" and thirst),

- red as a beet (flushing),

and - mad as a hen (central effects as delirium and agitation),

All the actions of atropine are present in an excessive manner.

Treatment:

1- Prevention of further exposure e.g., gastric lavage (if it is taken orally).

2- Symptomatic treatment as - cooling blankets for the fever,

- sympathomimetics for the hypotension,

and - diazepam for cerebral manifestations.

3- Physostigmine (a tertiary anticholinesterase) is given as it increases ACh which competes with the anticholinergic drugs at the muscarinic receptors. It antagonizes both peripheral and central effects because it can cross the blood brain barrier.

Dose: 0.01-0.03 mg/kg. It can be repeated after 15-30 minutes.

Differences between Anticholinergics

	Atropine	Scopolamine (Hyoscine)	Glycopyrrolate (Robinul)
Physical activity	<ul style="list-style-type: none"> • Tertiary amine, so it can cross blood brain barrier. • It is natural, derived from <i>Atropa belladonna</i> and <i>Datura Stramonium</i>. • Duration of action 30 minutes 	<ul style="list-style-type: none"> • Tertiary amine, so.... • It is natural, derived from <i>Hyoscyamus Niger</i>. 	<ul style="list-style-type: none"> • Quaternary amine, so it cannot cross blood brain barrier. • It is a synthetic atropine substitute. • Duration of action 2-4 hours.
Clinical differences <ul style="list-style-type: none"> • Tachycardia. • Antisialagogue. • Sedation (and other cerebral effects). • Antiemetic (in motion sickness) 	<ul style="list-style-type: none"> • +++ • ++ • + • + <p>Therefore, it is used as a premedication drug.</p>	<ul style="list-style-type: none"> • + • +++ • +++ • +++ <p>Therefore, it is used as a premedication drug and as an antiemetic in motion sickness.</p>	<ul style="list-style-type: none"> • ++ • +++ • - • - <p>(no cerebral actions) Therefore, it is used as a premedication drug.</p>
Doses	<ul style="list-style-type: none"> • I.v., i.m., or subcutaneous: 0.01-0.02 mg/kg up to 0.4-0.6 mg (an adult dose). • Oral 	<ul style="list-style-type: none"> • I.m.: the same dose of atropine. • Oral: 0.6 mg. • Transdermal patch 	<ul style="list-style-type: none"> • I.v. or i.m.: 1/2 the atropine dose.

Anticholinergic drugs are used to block the muscarinic symptoms of anticholinesterases during reversal of nondepolarizing muscle relaxants.

Other Atropine Substitutes

- Ipratropium bromide (*Atrovent*): is used as a bronchodilator. It is active topically as an aerosol with little systemic absorption. 1-2 puffs/6-8 hours (20 µg/puff) or by a nebulizer 2-3 mL of a solution containing 250 µg/mL.
- Benztropine (*Cogentin*): is used as an anti-parkinsonism drug.
- Hyoscine-N-butylbromide (*Buscopan*): is used as an anti-spasmodic agent in gastrointestinal tract.
- Clidinium (in *Librax*): is used as an anti-spasmodic agent.
- Metixene (in *Spasmocanulase*): is used as an anti-spasmodic agent.

DRUGS ACTING ON THE CARDIOVASCULAR SYSTEM

Vasodilators and Hypotensive Agents

Classification

a) Directly Acting Drugs on Smooth Muscles of the Blood Vessels:

- Drugs acting on the arterial and venous sides (mixed):
 - Na nitroprusside.
 - Trimethaphan or trimetaphan (*Arfonad*): It is no longer being manufactured.
 - Nicorandil (also coronary vasodilator).
- Drugs acting on the venous side (preload reducers):
 - Organic nitrates and nitrites (they are also coronary vasodilators).
- Drugs acting on the arterial side (afterload reducers):
 - K⁺ channel activators (Hydralazine, diazoxide, and minoxidil)
 - Adenosine.
 - Ca⁺⁺ channel blockers (they are also coronary vasodilators).

b) Neuro-Humoral Antagonists:

- Drugs acting on the arterial and venous sides:
 - α -blockers.
 - β_2 -agonists: as salbutamol.
 - Selective DA₁ agonist (Fenoldopam).
 - Angiotensin-converting enzyme inhibitors.
 - Phosphodiesterase inhibitors (enoximone, milrinone, and sildenafil).
 - Prostaglandins: epoprostenol (PGI₂) and alprostadil (PGE₁).

	Sodium Nitroprusside (SNP) (Nipride or Nipruss)	Organic Nitrates and Nitrites	Hydralazine (Aprisoline)
Mechanism of action	They bind to nitrate receptors in smooth muscles of vessel walls where they stimulate production of nitric oxide (NO) which is identical to the endothelial derived relaxing factor. The latter stimulates guanylate cyclase which in turn increases cyclic guanyl monophosphate (cGMP) , resulting in decreasing Ca ⁺⁺ influx and increasing Ca ⁺⁺ efflux. This leads to vasodilatation.	It is a venodilator mainly with little effect on arteries, leading to decreased preload.	It is a K⁺ channel activator (see later)
	It is an arteriodilator and venodilator , leading to a balanced decrease in the preload and afterload.		It is an arteriodilator mainly, with little effect on veins, leading to decreased afterload.
Pharmacokinetics	It is metabolized in red blood cells (RBCs) : <ul style="list-style-type: none"> • SNP enters RBCs where it receives (non-enzymatically) an electron from the iron of oxy-hemoglobin (Fe⁺⁺), resulting in unstable nitroprusside radical, which produces 5 cyanide ions (CN⁻), an active nitroso (N=O) group and met-hemoglobin. $\text{SNP} + \text{OxyHb} \rightarrow \text{met-Hb} + (\text{SNP})^-$ $(\text{SNP})^- \rightarrow 5 \text{CN}^- + \text{active nitroso group}$ • Cyanide ions (CN⁻) diffuse out to the plasma and pass in one of 3 reactions: <ol style="list-style-type: none"> 1) CN⁻ + met-Hb → Cyanmet-Hb 2) CN⁻ + thiosulfate $\xrightarrow{\text{Rhodanase}}$ Thiocyanate (slowly cleared by kidney). 3) CN⁻ + Cytochrome oxidase in tissues → interfere with O₂ utilization (cyanide toxicity). 	a) Nitroglycerine: <ul style="list-style-type: none"> • It is metabolized in the liver (mainly) and RBCs: it has a very high 1st pass effect where it is metabolized by glutathione organic nitrate reductase (rapid reductive hydrolysis), producing metabolites (one of them is nitrite which converts Hb Fe⁺⁺ to met-Hb Fe⁺⁺⁺). • T_{1/2} of nitroglycerine = 2-8 minutes. T _{1/2} of metabolites = 1-3 hours. b) Isosorbide dinitrate: <ul style="list-style-type: none"> • It is metabolized by the liver producing active metabolites (mononitrate) which share in the action. It has a long t_{1/2} = 4-6 hours. 	<ul style="list-style-type: none"> • It is metabolized in the liver by acetylation and hydroxylation.

	Sodium Nitroprusside (SNP) (Nipride or Nipruss)	Organic Nitrates and Nitrites	Hydralazine (Aprisoline)
Pharmacodynamic actions	<p>1- Venodilatation: decreases venous return and preload with decreasing left ventricular end diastolic pressure (LVEDP). This decreases myocardial work and O₂ demand which decreases the like-hood of ischemia.</p> <p>2- Arterio-dilatation: decreases afterload and left ventricular end systolic pressure (LVESP) which in turn,</p> <ul style="list-style-type: none"> • decreases wall tension and O₂ demand. • decreases blood pressure. This stimulates baroreceptor reflex, resulting in: <ul style="list-style-type: none"> - reflex tachycardia which is harmful in ischemic heart diseases and necessitates β blockers. - increased contractility and cardiac output, therefore; it can be used in congestive heart failure. <p>3- Coronary vasodilatation: may lead to coronary steal phenomenon with direction of coronary blood flow from the ischemic area (with maximally dilated diseases vessels) to normal areas (with normal blood vessels).</p>	<p>1- Venodilatation: As SNP. It is the main action.</p> <p>2- Slight arterio-dilatation: As SNP.</p> <p>3- Coronary vasodilatation:</p> <ul style="list-style-type: none"> • It increases blood flow directly to the ischemic areas. • It relieves coronary spasm. • It allows redistribution of coronary flow to the ischemic areas of the subendocardium. <p>These compounds produce their antianginal action through 1, 2, and 3.</p> <p>4- Relaxation of smooth muscles: of the bronchi (leading to broncho-dilatation), biliary tract, gastrointestinal tract, and uterus.</p>	<p>1- Slight venodilatation: As SNP.</p> <p>2- Arterio-dilatation: As SNP. It is the main action. It produces vasodilatation of renal vessels; therefore, it is used for patients with renal diseases.</p>
Side effects	<p>1- Due to vasodilatation:</p> <ul style="list-style-type: none"> • Arterio-dilatation causes severe hypotension, decreased cardiac output, and reflex tachycardia. The following occur: <ul style="list-style-type: none"> - Postural hypotension. - Overshooting i.e., marked unexpected reduction of blood pressure. - Rebound hypertension on sudden stoppage due to renin release during periods of hypotension (this can be blocked by β blockers or high epidural T₁ level block). • Cerebral vasodilatation abolishes cerebral autoregulation, but cerebral blood flow is increased or maintained unless marked drop of blood pressure occurs. This in turn increases intracranial tension especially in patients with decreased intracranial compliance (e.g., a brain tumor). This can be avoided by slow administration of the drug and by inducing hypocapnia. • Pulmonary vasodilatation causes: <ul style="list-style-type: none"> - decreased pulmonary artery pressure which leads to decreased perfusion of some normally ventilated alveoli. This increases the dead space. - prevention of the normal hypoxic pulmonary vasoconstrictive reflex. <p>Both lead to ventilation/perfusion mismatching, resulting in hypoxia.</p> <ul style="list-style-type: none"> • Meningeal vasodilatation causes throbbing headache. <p>2- Due to chronic usage: Tolerance is common.</p> <p>3- Met-hemoglobinemia It occurs on large doses and is treated by 1% methylene blue 1-2 mg/kg over 5 minutes. It converts met-Hb to normal Hb.</p> <p>4- Thiocyanate toxicity: It occurs especially in patients with renal failure resulting in mild toxic reactions such as thyroid hypofunction, hypoxia, nausea, muscle weakness, psychosis, and hallucinations.</p> <p>5- Acute cyanide toxicity: See later.</p>	<p>1- Due to vasodilatation: As SNP.</p> <p>Nitrates headache occurs frequently during the first few days of therapy with Isosorbide dinitrate. The patient should be encouraged to continue the medication (perhaps with administration of acetaminophen) because the headache frequently subsides with time and the antianginal efficacy of the long-acting nitrates persists.</p> <p>2- Due to chronic use: As SNP.</p> <p>3- Met-hemoglobinemia As SNP.</p>	<p>1- Due to vasodilatation: As SNP.</p> <p>2- Due to chronic use: Drug-induced lupus-like syndrome especially in slow acetylators.</p>

	Sodium Nitroprusside (SNP) (Nipride or Nipruss)	Organic Nitrates and Nitrites	Hydralazine (Apresoline)
Uses	1- Hypertensive emergency (crisis). 2- Controlled hypotension during anesthesia. 3- Refractory acute congestive heart failure (CHF) and acute pulmonary edema and congestion.	1- All types of angina. 2- Acute myocardial infarction. 3- Refractory acute CHF and acute pulmonary edema.	1- Hypertensive crisis. 2- Pregnancy associated hypertension. 3- Acute CHF or primary pulmonary hypertension.
Drug interactions	<ul style="list-style-type: none"> • SNP potentiates neuromuscular blockers because the reduction of blood pressure decreases the muscular blood flow (it is not due to a direct action). • Aminophylline potentiates the hypotensive effects of SNP due to inhibition of phosphodiesterase enzyme which increases cGMP. 	<ul style="list-style-type: none"> • They potentiate the neuromuscular blockade of pancuronium. • They should be used within 24 hours of sildenafil (Viagra), tadalafil (Cialis), or vardenafil (Levitra) use because this combination may produce severe hypotension. 	<ul style="list-style-type: none"> • It induces enflurane metabolism resulting in an increase in fluoride ion formation and its nephrotoxicity.
Doses and routes	<p>1- I.v. infusion:</p> <ul style="list-style-type: none"> - Onset: 1 minute. - Duration: 5 minutes. - The presentation: 5 mL-ampoule contains 50 mg. • For hypertensive crisis: 0.5-10 µg/kg/min. • For hypotensive anesthesia: 0.1- 0.5 µg/kg/min. - Calculation of the rate of infusion by syringe or infusion pump: see before. <p>2- I.v. bolus: (very rare)</p> <ul style="list-style-type: none"> • For decreasing the pressor response to intubation: 1- 2 µg/kg. <p>Precautions:</p> <ol style="list-style-type: none"> 1- Small doses should be chosen which are increased gradually at 2 minutes interval until the needed response is reached. 2- Infusions should not be stopped abruptly to avoid rebound hypertension. 3- Careful blood pressure monitoring (with invasive techniques) should be done during the therapy and after stopping the infusion. 4- The solution is unstable due to photo-degradation; therefore, <ul style="list-style-type: none"> • Once the drug is prepared, it must be used. • If the solution is discolored, it should be discarded. • It should be protected from the light by wrapping the bottles or syringes and i.v. lines in aluminum foil. 5- In liver and renal failure, on large doses, or prolonged usage > 2 days; plasma HCO₃, cyanide and thiocyanate levels should be assessed. 	<p>1- I.v. infusion:</p> <p>Nitroglycerine (<i>Tridil</i> or <i>Nitrocin</i>)</p> <ul style="list-style-type: none"> - Onset: 1 minute. - Duration: 5-10 minutes. - The presentation: 5 mL-ampoule contains 50 mg or 50 mL-ampoule contains 50 mg. - The dose ranges from 0.5-10 µg/kg/min. - Calculation of the rate of infusion by syringe or infusion pump: see before. <p>2- I.v. bolus: (very rare)</p> <ul style="list-style-type: none"> • For decreasing the pressor response to intubation: 1- 2 µg/kg. <p>Precautions:</p> <ol style="list-style-type: none"> 1, 2, and 3 are as SNP. 4- Nitroglycerine is absorbed by rubber and plastic bags (especially polyvinyl chloride "PVC"); therefore, glass containers and special i.v. tubing lines should be used. <p>Other routes:</p> <ul style="list-style-type: none"> ■ Nitroglycerine (glyceryl trinitrate): there are many forms as SL capsules (<i>Nitromack</i>), lingual spray, SL buccal tablets, SL oral form, ointment, and SL subcutaneous discs (<i>Nitroderm patch</i>). ■ Isosorbide dinitrate (<i>Isordil</i>, <i>Isomack</i> or <i>Dinitra</i>): SL tablets or capsules, chewable tablets, or oral sublingual tablets. ■ Isosorbide mononitrate: Oral tablets or SL capsules (<i>Effox</i>, or <i>Monomack</i>). ■ Amyl nitrite: Pearl for inhalation 	<p>1- I.v. bolus:</p> <ul style="list-style-type: none"> - Onset: 5-20 minutes. - Duration: 2- 4 hours. - The presentation: ampoule contains 20 mg powder diluted in 10 mL sterile water. - The dose ranges from 5-20 mg. Starts with 5- 10 mg repeated at 20- 30 min interval. <p>2- I.v. infusion: (rarely used due to its slow onset and long duration).</p> <p>0.25 - 1.5 µg/kg/min.</p> <p>3- Oral route:</p> <p>10 mg every 8- 12 hours.</p>

Side Effects of SNP: (cont.)Acute Cyanide Toxicity

- The rate of SNP breakdown to cyanide exceeds the rate of removal of cyanide from the plasma, resulting in increased cyanide which reacts with cytochrome oxidase in tissues. This interferes with O₂ utilization and causes **histo-toxic hypoxia**.
- It occurs **especially with impaired hepatic function** (not with impaired renal function) and **with large doses**, resulting in cumulation. Therefore, the maximum dose is 10µg/kg/min in acute usage and 4µg/kg/min in chronic usage.
- **Clinical picture:**
 - Metabolic acidosis.
 - Pink color skin.
 - Arrhythmias.
 - Increased venous O₂ content.
- **Tachyphylaxis** i.e., acute resistance to the hypotensive effect of increasing SNP dosage. It is an **early sign**.
- **Treatment:**
 - Mechanical **ventilation** with 100% O₂.
 - I.v. **sodium thiosulfate** 150 mg/kg over 15 minutes to increase SNP kinetics and combine with cyanide forming sodium thiocyanate, which is non-toxic compound cleared by the liver.
 - I.v. **3% sodium nitrate** 5 mg/kg over 5 minutes to oxidize Hb to met-Hb, which combine with cyanide and get rid of the latter.
 - I.v. **hydroxo-cobalamine** which combines with cyanide forming cyano-cobalamine (vitamin B12).

Potassium Channel ModulatorsA) Potassium Channel Openers (Activators)

They include hydralazine, minoxidil, and diazoxide.

Action:

They stimulate ATP-sensitive K⁺ channels in vascular smooth muscle cells, causing K⁺ efflux and membrane hyperpolarization. This leads to closure of calcium channels, and reduced intracellular calcium, with consequently vasodilatation.

Uses: They are used mainly as antihypertensive agents.

B) Potassium Channel Blockers

They include - Antiarrhythmic class III.

- Glibenclamide (an oral anti-diabetic drug)

NicorandilAction:

It acts as potassium channel activators and also increases nitric oxide release with an increase in cGMP leading to venodilatation and arterio-dilatation.

It acts also as a coronary vasodilator.

Uses: It is used mainly for the treatment of angina.

Adenosine (*Adenocard*)

It is a naturally occurring purine nucleoside.

Mechanism of Action:

It acts on specific adenosine receptors (in several vascular beds and on the SA node) (subtypes A₁-A₄), resulting in stimulation of adenylate cyclase enzyme which causes vasodilatation especially on the arterial side.

Pharmacokinetics:

It is metabolized rapidly (t_{1/2} = 10 seconds) by red blood cells and vascular endothelial cells to inosine and adenosine monophosphate.

It has a rapid onset = 15-30 seconds and its duration of effect lasts 1-2 min.

Pharmacological Actions and Side Effects:1- Cardiovascular Effects:

- **Arterio-dilatation:** of all blood vessels except renal vessels decreasing the afterload which decreases blood pressure **with reflex sympathetic activity**. The latter, in turn, increases heart rate, contractility, and cardiac output. Therefore, transient **facial flushing, light-headedness, palpitations, and hypotension** are common side effects.
- **Coronary vasodilatation (via A₂):** increases O₂ supply, but coronary steal phenomenon may occur. In patients unable to exercise, adenosine is used as a coronary vasodilator in combination with myocardial perfusion scanning to diagnose coronary artery diseases.

• **Antiarrhythmic action: class IVb:** It blocks AV conduction without compromising ventricular function and also decreases SA node automaticity on large doses which leads to short periods of sinus pause. It resolves spontaneously. Therefore, it is best avoided in patients with 2nd or 3rd degree heart block or with sick sinus syndrome. No tachycardia occurs.

2- Other Actions:

- Respiratory effects: - Pulmonary vasodilatation.
 - Bronchospasm (and dyspnea), so **contraindicated in bronchial asthma**.
 - Theophylline blocks adenosine receptors and antagonizes the actions of adenosine.
- Renal effects:

Adenosine-induced arterial hypotension inhibits renin release by the juxtaglomerular cells. Adenosine causes transient vasoconstriction of the afferent arterioles, combined with vasodilatation of the efferent arterioles. This **decreases renal blood flow and glomerular filtration** pressure and rate. There have been suggestions that this temporary decrease in renal function may play a protective role against an ischemic insult. A decrease in glomerular filtration rate is associated usually with a decrease in ultrafiltrate volume, reabsorption and oxygen demand. This protective effect is still not proved clinically.

Uses:

- 1- Hypertension.
- 2- Supraventricular arrhythmias including Wolf-Parkinson-White syndrome.

Drug Interactions:

- Dipyridamole and carbamazepine potentiate the action of adenosine.
- Aminophylline, caffeine and other methylxanthines antagonize adenosine competitively at the same receptors.

Dose and Route: (a 2 mL-ampoule contains 6 mg)

- 1- **I.v. infusion:** 60- 120 µg/kg/min. with an onset of 1 minute and a duration of 1 minute.
- 2- **I.v. bolus:** by **rapid injection (and flushed quickly by 20 mL saline)** of 6-12 mg over 1-2 seconds. It can be repeated once after 1-2 minutes.

N.B.: The dose should be decreased:

- to 1/3 to 1/5 the usual dose in patients with a transplanted heart because the transplanted heart is denervated.
- to 1/2 the usual dose in patients receiving calcium channel blockers, β-blockers, or dipyridamole, or when adenosine is injected into a central vein such as the superior vena cava (due to the risk of asystole when the standard doses are injected via a central vein).

Calcium Channel Blockers

Classification:

- 1- Phenylalkylamines: 1st generation: - Verapamil (*Isoptin, Verapamil, Veratens, Calan, Coer, Covera or Cardiomil*).
- 2- Benzothiazepines: 1st generation: - Diltiazem (*Altiazem, Delay-tiazem, Cardiazem, Dilacor, Tiazac, or Peltiazem*).
- 3- Dihydropyridines: - 1st generation: Nifedipine (*Epilat, Procardia or Adalat*).
 - 2nd generation: Nicardipine (*Micard, Cardene or Pelcard*)
 - Nimodipine (*Nimotop*).
 - Felodipine (*Plendil, or Plentopine*)
 - Isradipine (*Dynacirc*).
 - Nisoldipine (*Sular*).
 - 3rd generation: Lacidipine (*Lacipil*).
 - Amlodipine (*Norvasc, Alkapress, Vasonorm, or Amilo*)

Mechanism of Action:

- Calcium channel blockers bind to different specific binding sites on the **α₁- subunit of the L-type of voltage-gated Ca⁺⁺ channels**, leading to decreased Ca⁺⁺ influx in response to action potential. They bind more strongly in depolarized tissues (ischemic or infarcted tissues).

Ca⁺⁺ entry into the cell induces further Ca⁺⁺ release from the sarcoplasmic reticulum, which facilitates conduction of the cardiac action potential and excitation-contraction coupling by interaction with calmodulin (in smooth muscle) or troponin (within cardiac muscle). Ca⁺⁺ channel blockers prevent this Ca⁺⁺ entry and so produce inhibition of excitation-contraction coupling, causing decreased myocardial contractility.

- **Dihydropyridines** block the channels extracellularly from **the outer surface (i.e., plugging)** in an all or none fashion.
- **Phenylalkylamines (e.g., verapamil)** block the channels intracellularly from **the inner surface** of the membrane resulting in changing the kinetics of activation and recovery of Ca^{++} channels.
- **Benzothiazepines (e.g. diltiazem)** act on the α_1 subunit, but the mechanism is not fully understood.

N.B.: **Ca^{++} Enters the Cells by 3 Main Mechanisms:**

- Voltage-gated Ca^{++} channels: in excitable cells; they open on depolarization (the most important route of entry). There are 5 types:
 - L-channel (long-acting): in cardiac and smooth muscles. It causes slow Ca^{++} influx during the plateau of the action potential. It is stimulated by catecholamines and blocked by Ca^{++} channel blockers.
 - T-channels: regulate the rhythmic activity and action potential firing patterns.
 - N-, Q-, and P-channels: are mainly for neurotransmitter release.
- Receptor-operated Ca^{++} channels: in excitable and non-excitable cells. They open by receptor agonists.
- Stretch-activated channels.
- Na^+ and Ca^{++} exchange mechanism.

Pharmacological Action

First-Generation

	Verapamil	Diltiazem	Nifedipine
Pharmacokinetics: Elimination half-life (h)	5-8	2-6	3-5
Route of elimination	Renal and hepatic	Hepatic	Renal and hepatic
Pharmacodynamics 1- Cardiac :			
• SA node:	• Negative chronotropic	• Negative chronotropic	• no chronotropic effect, but there is reflex tachycardia
• Contractility:	• Negative inotropic. It does not decrease cardiac output due to the associated decreased in afterload.	• Negative inotropic, but less effect is produced.	• No or little effect.
• AV node:	• Negative dromotropic action (i.e., anti-arrhythmic class IVa). It increases conduction in the accessory tract; so, contraindicated in Wolf-Parkinson-White syndrome.	• Negative dromotropic	• No dromotropic action (i.e., there is no antiarrhythmic action).
• Cytoprotective action	They protect the myocardial and cerebral tissues from the damaging effect of ischemia due to decreasing the intracellular Ca^{++} during ischemia and these decreasing tissue excitability and also decreasing the metabolic needs of cells.		• No evidence.
2- Vascular:			
• Arterial vasodilatation	+, but no reflex tachycardia	++, but no reflex tachycardia.	+++ , with reflex tachycardia and increased cardiac output.
• Coronary dilatation	+	+	+++
3- Other actions	• Relaxation of smooth muscles of the uterus, bronchi, and esophagus. • Inhibition of platelet aggregation		• It produces vasodilatation of renal vessels, increasing renal blood flow. This causes diuresis.
Uses: All agents are used in treatment of hypertension and angina.	• Treatment of paroxysmal supraventricular tachyarrhythmias and atrial fibrillation. • Hypertrophic obstructive cardiomyopathy. • Primary pulmonary hypertension.		• Peripheral vascular diseases as Raynaud's disease. • During renal transplantation
Doses	Oral: 80-160 mg/8 hours I.v.: 75-150 μg /kg slowly over 2 minutes	Oral: 30-90 mg/8 hours I.v.: 75-150 μg /kg slowly over 2 minutes	Oral: 10-40 mg/8 hours I.v.: 3-15 μg /kg slowly

2ND and 3RD Generations

	Nicardipine	Nimodipine	Felodipine	Amlodipine	Lacidipine
Pharmacokinetics: Elimination half-life (h)	3-8		25 (long acting drug)	35-50 (long acting drug)	13-19
Route of elimination	Renal and hepatic		Renal and hepatic	Renal	Renal and hepatic
Pharmacodynamics 1- Cardiac: • SA node, contractility, and AV node.	• All the 2 nd and 3 rd generations have no effect on the SA node and the AV node, and contractility, unlike verapamil and diltiazem.				
2- Vascular: • Arterial vasodilatation	++, with minimal reflex tachycardia	++, with minimal reflex tachycardia	+++ with minimal reflex tachycardia	+++ with no reflex tachycardia	++++, with no reflex tachycardia
• Coronary dilatation	+++	+/-	+	++	+/-
3- Other actions	• They are selective in producing cerebral vasodilatation		• They produce renal vasodilatation with mild diuretic and natriuretic actions.		• It is sequestered in the lipid bilayer of vascular smooth muscle cells and delays the development of atherosclerosis. It increases the action of NO which has vasodilator, anti-platelet, and anti-proliferative actions.
Uses: in treatment of hypertension and angina	• Cerebral vasospasm in subarachnoid hemorrhage.		• Heart failure.		

Side Effects

- 1- Hypotension: - in verapamil and diltiazem; bradycardia and heart block also occur.
- in nifedipine; reflex tachycardia occurs.
- in 2nd generation: minimal tachycardia occurs.
- in 3rd generation, no tachycardia occurs.
- 2- Ankle edema, flushing, and headache due to vasodilatation.

Drug Interactions

- 1- Ca⁺⁺ channel blockers especially verapamil, potentiate:
 - digoxin and theophylline due to decreased hepatic metabolism.
 - the hypotensive effects of volatile agents.
 - the anesthetic effect of halothane and decrease the MAC.
 - the depolarizing and non-depolarizing muscle relaxants.
- 2- With β - blockers and volatile agents: especially verapamil and diltiazem; bradycardia, heart block, and myocardial depression occur.

Angiotensin-Converting Enzyme (ACE) Inhibitors**Physiological Considerations**

Angiotensin-II (AT-II) is produced from angiotensinogen in the walls of small blood vessels in the lungs, kidneys, and other organs and in the plasma (figure 4-7):

AT-II acts on 4 subtypes of angiotensin receptors:

- **AT₁ receptors:** are present mainly in the vascular smooth muscles, adrenal cortex, kidney, liver, and some areas of the brain. It acts via Gq protein where it increases intracellular Ca⁺⁺. It causes most of the actions of AT-II.
- **AT₂ receptors:** are present in the kidney, adrenal medulla, uterus, ovary and the brain. They play a role in cell growth and differentiation.
- **AT₃ receptors:** have unclear roles.

Actions of AT-II:

- Direct effect: arteriolar and venoconstriction.
 - Sodium reabsorption by direct action at the proximal tubules and by increased aldosterone production.
 - Increased aldosterone production.
 - Sympathetic nervous system activation by direct action and indirect action by increased release of noradrenaline and adrenaline and may inhibit cardiac vagal activity.
 - Increased erythropoiesis.
 - Direct trophic action on vascular smooth muscles and cardiac muscle, promoting cellular proliferation and hypertrophy.
 - Other effects e.g., controlling regional blood flow in some vascular beds as the splanchnic vessels.
- Therefore, AT-II has a major role during compensation of heart failure.

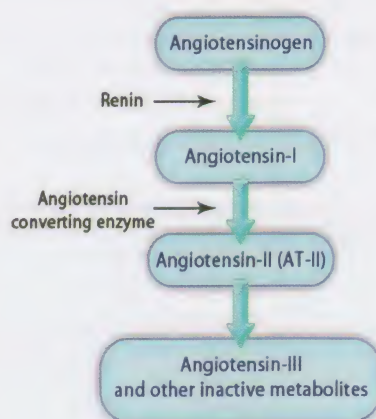


Figure 4-7: Synthesis of angiotensin II

Drugs Acting on the Renin-Angiotensin System**1- Suppression of Renin Release or Inhibition of Renin Activity:**

Sympatholytic drugs as β - blockers or central α -antagonists: they inhibit renin secretion which in turn inhibits production of AT-II, but their effect is limited due to reduction of AT-II production, which stimulates more renin secretion.

2- Inhibition of Angiotensin Converting Enzyme (ACE):

ACE inhibitors.

3- Blockade of AT-II Receptors:

AT₁-receptor blockers: they noncompetitively block AT₁ receptors and inhibit the renin-angiotensin system independently from the AT-II.

4- Aldosterone Antagonism:

Spironolactone and eplerenone: are competitive inhibitors of aldosterone at renal mineralo-corticoid receptors.

ACE Inhibitors**Mechanism of Action:**

Inhibition of ACE causes:

- Decreased renin-angiotensin-aldosterone system, resulting in:
 - **Decreased angiotensin-II;** this leads to - **arteriodilatation** (i.e., decreased afterload).
 - **venodilatation** (i.e., decreased preload)

So, they improve cardiac output without an increase in heart rate.

 - **Decreased aldosterone secretion;** this leads to **decreased salt and water retention.**
 - **Increased vasodilators** such as **bradykinin and other kinins, prostaglandins, endorphins, and substance P.**
- N.B.: ACE is the same enzyme as Kininase II and is involved in the metabolism of both Kinins and prostaglandins; therefore, its inhibition increases these substances).
- **Decreased ventricular remodelling** (i.e., ventricular dilation and hypertrophy) and even producing "reverse-remodelling" phenomenon.

Uses:

- 1- Refractory congestive heart failure. They are now considered the first line of treatment of heart failure.
- 2- High renin hypertension such as unilateral renal artery stenosis, renal failure, and diabetic nephropathy.
- 3- Hypertension emergencies such as malignant hypertension and hypertensive encephalopathy. I.v. enalaprilat (the active form of enalapril) is the one used in emergencies.

Agents:

- Captopril (*Capoten, Hypopress, Lotensine, or Capozide* with Hydrochlorothiazide).
- Lisinopril (*Lisopril, Prinivil, Sinopril, Zestril, or Zestoretic* with hydrochlorothiazide).
- Enalapril (*Acapril, Ezapril, Renitec, Vasotec, or Lotrial*).
- Fosinopril (*Monopril, or Monozide* with hydrochlorothiazide).
- Perindopril (*Coversyl, or Aceon*).
- Ramipril (*Corpril, Altace, Ramipril, Tritace, or Tritace comp* with hydrochlorothiazide).
- Benzapril (*Cibacin, Lotensin, or Cibadrex* with Hydrochlorothiazide)
- Trandopril (*Mavik, Tarka* with verapamil).
- Moexipril (*Univasc*).
- Quinapril (*Accupril*).

Captopril and lisinopril are active drugs but all the others are prodrugs.

All agents are eliminated by the kidneys except trandopril and fosinopril that are eliminated by both the kidneys and the liver.

Side Effects:

- 1- **1st dose phenomenon:** i.e., profound hypotension with the 1st dose especially in hypovolemic or sodium-depleted patients; therefore, the therapy should be started with the smallest possible dose and increased gradually.
- 2- **Renal insufficiency:** especially - if renal perfusion is decreased (e.g., due to renal artery stenosis, congestive heart failure, or hypovolemia),
 - in geriatric patients,
 - in those receiving non-steroidal anti-inflammatory drugs.

Therefore, renal function should be checked before starting ACE inhibitors, and monitored subsequently.

- 3- **Hyperkalemia** due to decreased aldosterone concentrations especially in patients with renal impairment, or in patients taking potassium supplements or potassium sparing diuretics.
- 4- **Dry cough, angioneurotic edema, and skin rash** due to accumulated bradykinin and prostaglandins which stimulate the nerves (ACE is a kininase; therefore, inhibiting this enzyme, which normally degrades bradykinin, with an ACE inhibitor leads to increased kinin levels; an effect not seen with an angiotensin II receptor antagonist).
- 5- **Respiratory side effects:** upper respiratory congestion or rhinorrhea.
- 6- **Gastrointestinal disturbances.**
- 7- **Hyperglycemia** in diabetic patients.
- 8- **Taste disturbances,** and neutropenia.
- 9- **Contraindicated in pregnancy.**
- 10- **The incidence of hypotension during anesthesia is increased** in patients on ACE inhibitors, so some physicians prefer to **stop ACE inhibitors before surgery** if significant blood loss or fluid shifts are likely.

AT₁ Receptor Blockers**Action:**

They **block angiotensin II (AT₁) receptors noncompetitively**, inhibiting renin-angiotensin-aldosterone system independently. Therefore, a compensatory increase in renin secretion occurs.

They have no effects on bradykinin or prostaglandins; so, no dry cough, angioneurotic edema or skin rash occur.

- Cardiovascular effects: they decrease the afterload, resulting in an increase in the cardiac output without tachycardia.
- They increase uric acid secretion i.e., a uricosuric action.

Uses:

- Hypertension.
- Diabetic nephropathy.
- Heart failure.

Agents:

- Losartan (*Amosar, Cozaar, Kanzar, Losar, Lozapress, Remtozar, or Fortzaar* and HyzAAr with

hydrochlorothiazide).

- Candesartan (*Atacand* or *Candesar*).
- Valsartan (*Diovan*, *Disartan*, *Tareg*, or *Co-Tareg* and *Co-Diovan* with hydrochlorothiazide)
- Telmisartan (*Micardis*).
- Eprosartan (*Teveten*).
- Irbesartan (*Avapro*).
- Olmesartan (*Binicar*).

- Both losartan and candesartan are prodrugs.

- Losartan, candesartan, and irbesartan are eliminated by the kidney and the liver.

Valsartan, eprosartan, and telmisartan are excreted in the bile mainly.

Side Effects:

- **Hyperkalemia** due to decreased aldosterone concentration especially in patients with renal impairment, or in patients taking potassium supplements or potassium sparing diuretics.
- **Contraindicated in pregnancy.**

Antiarrhythmic (Anti-dysrhythmic) Drugs

Classification of Antiarrhythmic Drugs

(The Vaughan Williams Classification)

It classifies the antiarrhythmic drugs according to the electrophysiological mechanisms. This classification has limitations such as:

- Some drugs belong to more than one class.
- Some other drugs e.g., digoxin do not fit into the classification. Some consider the digoxin class V.

Class	Agents	Action	Uses
Class I	Sodium channel blockers (membrane stabilizers)		
Ia	<ul style="list-style-type: none"> • Quinidine (<i>Quinacard</i>) • Procainamide (<i>Pronestyl</i>) • Disopyramide (<i>Norpace</i>) • Ajmalin <p>N.B.: Bidisomide has Ia/Ib action</p>	<p>1- They have intermediate (between Ib and Ic) onset/offset kinetics i.e., they have intermediate association and dissociation to Na⁺ channels (during that Na⁺ channels are blocked). This causes:</p> <ul style="list-style-type: none"> • prolongation of the effective refractory period (ERP) • a moderate decrease or delay in conduction velocity (i.e., increased conduction time) • an increase in action potential duration • a moderate phase 0 depression (i.e., decreased depolarization and V_{max}). <p>2- The same actions occur in accessory bundles (His-Purkinje system and Kent bundles) as in Wolf-Parkinson-White (WPW) syndrome.</p> <p>3- They decrease abnormal automaticity (especially in ectopic foci) due to:</p> <ul style="list-style-type: none"> • decreased slope of phase 4 depolarization • shifting of threshold voltage potentials towards zero. <p>4- They decrease excitability due to local anesthetic actions.</p> <p>5- They have a negative inotropic action.</p> <p>6- ECG changes are dose-dependent; they include:</p> <ul style="list-style-type: none"> • QTc interval prolongation. • QRS widening. • ST segment depression. • T wave inversion. • U wave appearance. <p>They may induce torsades de pointes (a form of polymorphic ventricular tachycardia).</p> <p>7- They have an anticholinergic (atropine-like) and sympathomimetic action.</p>	<p>Broad spectrum as in</p> <ul style="list-style-type: none"> • Paroxysmal supra-ventricular tachycardia. • Atrial flutter and atrial fibrillation. • Ventricular tachycardia. • Ventricular extrasystoles. • WPW syndrome.
Ib	<ul style="list-style-type: none"> • Lignocaine (<i>Xylocard</i>) • Phenytoin (<i>Epanutin</i>) • Mexiletine (<i>Mexitil</i>) • Tocainide (<i>Tonocard</i>) <p>N.B.: Morizine (<i>Ethmozine</i>) has Ib/Ic actions</p>	<p>1- They have rapid onset/offset kinetics; therefore,</p> <ul style="list-style-type: none"> • They attach to Na⁺ channels very rapidly after depolarization; so, at the beginning of diastole, there are insufficient drug free channels available to respond to a stimulus resulting in prolongation of ERP. • They dissociate from Na⁺ channels very rapidly; so, at the end of diastole, nearly all channels are again drug-free. This causes: <ul style="list-style-type: none"> - no or minimal decrease in conduction velocity of normal tissues - minimal or mild phase 0 depression (V_{max}) - a marked decrease in action potential duration due to rapid repolarization. <p>2- In ischemic tissues, they decrease conduction velocity markedly, but in depolarized tissues (by stretching or decreased extracellular K⁺), they increase the conduction velocity; therefore, reentry circuits</p>	<ul style="list-style-type: none"> • Ventricular arrhythmias. • Digitalis induced ventricular arrhythmias.

		<p>due to the presence of ischemic or depolarized tissues are abolished.</p> <p>3- They decrease automaticity in purkinje fibers (no effect on SA node) as they decrease the slope of phase 4 depolarization.</p> <p>4- They decrease excitability in purkinje fibers as they increase K^+ conduction.</p> <p>5- ECG changes are minimal such as shortening of QT interval (there is no widening of QRS complex).</p>	
	<ul style="list-style-type: none"> • Flecainide (<i>Tambacor</i>) • Propafenone (<i>Rytmonorm</i> or <i>Rythmol</i>) • Encainide. • Lorcainide 	<p>1- They have slow onset/offset kinetics; therefore,</p> <ul style="list-style-type: none"> • They attach to Na^+ channels very slowly after depolarization. So at the beginning of diastole, there are sufficient drug free channels available to respond to a stimulus, resulting in no prolongation of ERP. • They dissociate from Na^+ channels very slowly; so, at the end of diastole, some channels are still occupied by the drug. This causes: <ul style="list-style-type: none"> - a marked decrease in conduction velocity - a marked phase 0 depression (V_{max}) - no change in action potential duration. <p>2- ECG changes are present such as QRS widening.</p>	Broad spectrum
Class II	B- blockers		
	<ul style="list-style-type: none"> • Propranolol (<i>Inderal</i>) • Metoprolol (<i>Lopressor</i>) • Acebutol • Esmolol (<i>Brevibloc</i>) <p>N.B.: Sotalol has class II/III actions.</p>	<p>1- ERP is minimally (or not) affected.</p> <p>2- AV conduction velocity is decreased.</p> <p>3- Accessory pathways conduction is minimally (or not) affected.</p> <p>4- The automaticity is decreased (this is the main action) due to a decrease in the slope of phase 4 depolarization at the SA and AV nodes.</p> <p>5- They decrease the effect of catecholamines on the heart i.e., they decrease the sympathetic effects on the heart.</p>	<ul style="list-style-type: none"> • Supra-ventricular arrhythmias especially due to exercise or thyrotoxicosis, or these sympathetically induced. • Digitalis induced ventricular arrhythmias
Class III	Potassium channel blockers (Repolarization inhibitors)		
	<ul style="list-style-type: none"> • Amiodarone (<i>Cardiomep</i>, <i>Cordarone</i>) • Bretylium • Sotalol (<i>Betapace</i>) (with class II actions) • Ibutilide (<i>Corvert</i>) • Dofetilide (<i>Tikosyn</i>) 	<p>1- They inhibit K^+ influx, resulting in prolongation of ERP and action potential.</p> <p>2- AV conduction velocity is decreased.</p> <p>3- The same actions occur in accessory bundles.</p> <p>4- The automaticity is decreased in the SA node and AV node due to a decrease in the slope of phase "4" depolarization of the SA and AV nodes.</p> <p>5- ECG changes are absent.</p>	<ul style="list-style-type: none"> • Amiodarone is broad spectrum. • Bretylium acts on ventricular arrhythmias. • Sotalol acts on supra-ventricular arrhythmias.
Class IVa	Calcium channel blockers		
	<ul style="list-style-type: none"> • Verapamil • Diltiazem 	<p>1- They prevent Ca^{++} influx during the plateau of the action potential by blocking L-type Ca^{++} channels, resulting in prolongation of ERP.</p> <p>2- AV conduction is decreased.</p> <p>3- There is a minimal effect on the conduction of accessory bundles.</p> <p>4- There is a decrease in action potential duration.</p>	<ul style="list-style-type: none"> • Supraventricular arrhythmias.
Class IVb	Potassium channel openers		
	<ul style="list-style-type: none"> • Adenosine (<i>Adenocard</i>) • Aprikalim • Bimakalim • Cromokalim 	<p>1- They activate ATP regulated K^+ channels resulting in increased K^+ influx. This causes hyperpolarization and inhibition of voltage dependent Ca^{++} channels, leading to decreased Ca^{++} entry which in turn decreases the force of contraction.</p> <p>2- AV conduction is decreased.</p> <p>3- The same effect in accessory bundles.</p> <p>4- Automaticity is decreased.</p>	<ul style="list-style-type: none"> • Supraventricular arrhythmias.

Individual Antiarrhythmic Drugs

	Quinidine	Procainamide	Disopyramide	Phenytoin (Diphenyl hydantoin)
Actions	<p>A) Cardiac actions</p> <ul style="list-style-type: none"> • Class Ia actions. • Mild negative inotropic action. <p>B) Autonomic actions:</p> <ul style="list-style-type: none"> • Moderate anticholinergic action. • α-blocking actions, resulting in vasodilation and a decrease in blood pressure with reflex sympathetic stimulation and increased heart rate. <p>C) other actions:</p> <ul style="list-style-type: none"> • Antipyretic action • Anti-malarial actions. • Skeletal muscle relaxant action so contraindicated in myasthenia gravis. 	<p>A) Cardiac actions:</p> <ul style="list-style-type: none"> • Class Ia actions. • Moderate negative inotropic action. <p>B) Autonomic actions:</p> <ul style="list-style-type: none"> • Weak anticholinergic action. • Ganglion blocking action. 	<p>A) Cardiac actions:</p> <ul style="list-style-type: none"> • Class Ia actions. • Marked negative inotropic action. <p>B) Autonomic actions:</p> <ul style="list-style-type: none"> • Marked anticholinergic action. 	<p>A) Cardiac actions:</p> <ul style="list-style-type: none"> • Class Ib actions. <p>B) Autonomic actions:</p> <ul style="list-style-type: none"> • A central decrease in sympathetic activity of the heart caused by digitalis toxicity. <p>C) Antiepileptic action: It inhibits development and spread of seizure activity by:</p> <ul style="list-style-type: none"> • Blocking voltage-sensitive Na^+ channels reducing Na^+ influx and increasing Na^+ efflux. • Decreasing Ca^{++} influx. <p>This leads to stabilization of the neuronal membrane.</p>
Pharmacokinetics	<ul style="list-style-type: none"> • Eliminated by the liver (80%) and kidney (20%) as active metabolites. • Elimination $t_{1/2}$ = 5-8 hours. 	<ul style="list-style-type: none"> • Eliminated by the liver (50%) and kidney (50%) as active metabolites. • Elimination $t_{1/2}$ = 3-5 hrs. 	<ul style="list-style-type: none"> • Eliminated by the liver (50%) and kidney (50%) as inactive metabolites. • Elimination $t_{1/2}$ = 4-6 hrs. 	<ul style="list-style-type: none"> • Eliminated by the liver (95%) and kidney (5%) as inactive metabolites. • Elimination $t_{1/2}$ = 6-32 hours.
Side effects	<p>It has a low therapeutic index</p> <p>1- Cardiac:</p> <ul style="list-style-type: none"> • Heart block. • Quinidine syncope (sudden arrhythmogenic death): attacks of fainting due to torsades de pointes or ventricular fibrillation. • It precipitates heart failure. • Increased digitalis toxicity. <p>2- Gastrointestinal upset.</p> <p>3- Cinchonism: tinnitus, loss of hearing, and blurred vision.</p> <p>4- Allergic reactions as fever, thrombocytopenia, and anaphylactic shock.</p>	<p>1- Cardiac:</p> <p>As quinidine, but precipitation of heart failure is more common and it does not increase serum digoxin level.</p> <p>2- Gastro-intestinal upset.</p> <p>3- Allergic reactions as drug fever, agranulocytosis, skin rash, and systemic lupus erythematosus.</p>	<p>1- Cardiac:</p> <p>As quinidine.</p> <p>2- Gastro-intestinal upset.</p> <p>3- Anti-cholinergic actions as dry mouth...etc.</p>	<p>1- Cardiac:</p> <ul style="list-style-type: none"> • Rapid i.v. injection causes hypotension, bradycardia and respiratory arrest. <p>2- Allergic reaction (on chronic use) as hepatitis, systemic lupus, and megaloblastic anemia.</p> <p>3- Gum hyperplasia.</p> <p>4- Neurological: nystagmus, ataxia, diplopia and vertigo.</p> <p>5- Gut upset as nausea, vomiting and anorexia.</p> <p>6- Teratogenic: especially cleft palate.</p> <p>7- Osteomalacia and hypocalcemia.</p> <p>8- Hirsutism and acne due to inhibition of androgen release.</p> <p>9- Thrombophlebitis after i.v. intake because it is prepared in propylene glycol which is very irritant.</p> <p>10- Drug interaction:</p> <ul style="list-style-type: none"> • Phenylbutazone, sulphonamide, aspirin, valproic acid displaces phenytoin from plasma proteins. • Chloramphenicol, dicumarol, isoniazid, sulphonamide, cimetidine, and valproic acid inhibit phenytoin metabolism. • Carbamazepine and phenobarbitone stimulate phenytoin metabolism. • Phenytoin is an enzyme inducer which increases the metabolism of warfarin, steroids, digitoxin, and oral contraceptives.
Doses	<p>1- Oral: 200 mg/6 hours.</p> <p>2- I.v. slowly 5-10 mg/kg.</p>	<p>1- Oral: 500-1000 mg/4 hrs.</p> <p>2- I.v. slowly: 5-10 mg/kg then infusion 1-4 mg/min.</p>	<p>1- Oral: 100-150 mg/6 hours</p> <p>It is not available as intravenous injection.</p>	<p>1- I.v.: loading 5-15 mg/kg then maintenance by oral route.</p> <p>2- I.v. for status epilepticus and arrhythmias: 100 mg/5 minutes with a maximum of 1 g.</p> <p>3- Oral: 400 mg/day</p> <p>Therapeutic range: 10-20 Pg/mL.</p>

	Lignocaine or lidocaine	Flecainide	Propafenone	Amiodarone	Bretylium
Actions	A) Cardiac actions: • Class Ib action B) There is no autonomic action. C) Others: it has a local anesthetic action .	A) Cardiac actions: • Class Ic action B) There is no autonomic action.	A) Cardiac actions: • Class Ic action • Mild Ca⁺⁺ channel blocking action (as class IVa). B) Autonomic action: • Weak β blocking action (as class II).	A) Cardiac actions: • Class III action • Weak Ca⁺⁺ channel blocking action (as class IVa) • Effective Na⁺ channel blocking action. B) Autonomic action: • Vasodilatation of coronary and peripheral vessels.	A) Cardiac actions: • Class III action B) Autonomic action: • It is an adrenergic neuronal blocker which decreases noradrenaline uptake resulting in positive inotropic action and hypertension.
Pharmacokinetics	• Eliminated by the liver (95%) and kidney (5%) as active metabolites (monoethyl-glycine-xylodide "MEGX") . • Elimination $t_{1/2}$ = 1-2 h.	• Eliminated by the liver (60%) and kidney (40%) to active metabolites . • Elimination $t_{1/2}$ = 11 h.	• Eliminated by the liver mainly . • Elimination $t_{1/2}$ is variable.	• Eliminated by the liver mainly as active metabolites (desethyl-amiodarone) . • Elimination $t_{1/2}$ is long = 30-90 days. It is structurally similar to thyroxine and procainamide.	
Side effects	1- Cardiac: in ischemic heart, SA node standstill may occur together with impairment of AV conduction. 2- Perioral numbness, tremors, dizziness, confusion up to convulsion with toxic doses (see local anesthetic toxicity). 3- Decreased hepatic blood flow or cimetidine increases lidocaine levels.	1- Cardiac: • All class Ic are pro-arrhythmogenic i.e., they can increase cardiac arrhythmias. • It precipitates heart failure. 2- Central nervous system symptoms as dizziness.	1- Cardiac: bradycardia 2- Central nervous system symptoms as Flecainide. 3- Gastro-intestinal upset. 4- Allergic reactions as systemic lupus.	1- Cardiac: bradycardia, hypotension, and heart block. 2- Ocular: corneal micro-deposits and photosensitivity. 3- Hypo- or hyper-thyroidism. 4- Proximal myopathy and neuropathy. 5- It increases serum digoxin, warfarin, heparin, procainamide, disopyramide, propafenone and quinidine levels. 6- Avoid co-administration with other drugs which prolong the QT interval e.g., diltiazem, verapamil, phenothiazines, sotalol or class Ia.	1- Gastro-intestinal upset. 2- Postural hypotension. 3- Parotid gland swelling.
Doses	I.v.: loading 1-2 mg/kg then i.v. infusion 2-4 mg/min.	Oral 100 mg/12 hours	1- Oral: 450-900 mg/day. 2- I.v. 1-2 mg/kg	1- Oral: (200 mg/tablet) Loading 800-1200 mg once/day for 2-4 weeks then maintaining at 200-800 mg/day. 2- I.v. 5-10 mg/kg over 5 minutes followed by i.v. infusion of 900 mg over 24 hours.	I.v. slowly over 5 minutes Loading: 5-10 mg/kg Maintenance: 1-2 mg/min.

Mexiletine

It is similar to lignocaine but it is of a longer duration and is taken orally.

Other Antiarrhythmic Drugs

Magnesium Sulphate

Action:

- It is a co-factor for many enzyme systems, including the myocardial Na⁺/K⁺ ATPase.
- It antagonizes atrial L and T type Ca⁺⁺ channels, so prolongs both the atrial refractory periods and conduction.
- It inhibits K⁺ entry and suppresses ventricular after-depolarizations.

Uses:

- 1- It is the treatment of choice for **torsades de pointes**, a type of ventricular tachycardia induced by class Ia or class III antiarrhythmic drugs with prolongation of QT interval.
- 2- It is the second line of treatment of **supraventricular and ventricular arrhythmias**, particularly those associated with **digoxin toxicity or hypokalemia**.
- 3- As an anticonvulsant in patients with **pre-eclampsia**.
- 4- **Severe refractory acute bronchial asthma**. Some consider it the first line in treatment in severe asthma.

Pharmacokinetics:

It is redistributed rapidly into bone (50%) and intracellular fluid (45%) while the remainder is excreted via the kidneys (5%).

Side Effects: See later in the chapter of "obstetrics".

Doses:

- As an antiarrhythmic: 8 mmol over 15 min followed by continuous i.v. infusion of 0.5-3 mmol/h.
- As a bronchodilator: 16 mmol over 30 min followed by continuous i.v. infusion of 4-8 mmol/h.

Cardiac Glycosides (Digitalis)

Chemical Structure

They are derived from plant sources, principally *Digitalis purpurea* and *Digitalis lanata*. They consist of:

a- Aglycone (genin):

- It is formed of a steroid nucleus and an unsaturated lactone ring.
- It is responsible for the pharmacodynamic effect (i.e., the pharmacological active part).

b- Sugar:

- It is usually digitoxose.
- It is responsible for the pharmacokinetic effect (i.e., solubility and potency).

Both are linked by an ether linkage (Oxygen Bridge).

Pharmacokinetics

	Digitoxin	Digoxin	Quabain
• Lipid solubility	• High	• Medium	• Low
• Elimination $t_{1/2}$	• 7 days	• 1.7 days (36 hours)	• 21 hours.
• Enterohepatic circulation	• 27%	• 7%	• -
• Elimination	• hepatic 90%, renal and stool	• Renal >80%, hepatic 20%	• Renal mainly.
• Onset of action	• I.v.: 4-8 hours	• Oral: 1.5-6 hours I.v.: 5-30 min	• I.v.: 10 min

Pharmacodynamic Action:**A) Mechanical Effects:**

They produce **positive inotropic action** (direct action).

Mechanism:

1- Digitalis inhibits membrane-bound Na^+/K^+ ATPase by competitive binding to the K^+ binding sites of ATPase, resulting in increased intracellular Na^+ . This leads to:

- An increase of exchange of intracellular Na^+ for extracellular Ca^{++} .
- Displacement of Ca^{++} from its binding sites.

2- It directly stimulates voltage-dependent Ca^{++} channels leading to increased Ca^{++} entry.

3- It releases Ca^{++} from the sarcoplasmic reticulum.

Therefore, there is an increase in the intracellular Ca^{++} which binds with troponin, leaving actin to slide on myosin which increases contractility (figure 4-8).

The positive inotropic action **increases cardiac output**. This leads to:

- A decrease in end-diastolic volume and pressure, reducing venous return and heart size.
- Improvement of the circulation with a compensatory decrease in sympathetic activity, so both the preload and afterload are decreased causing a further increase in the cardiac output.
- An increase in renal blood flow which increases glomerular filtration rate. This produces diuresis and decreases aldosterone secretion which improves the peripheral edema.

N.B.: The diuretic action of digitalis is due to:

- the increased cardiac output which improves renal blood flow as above,
- decreased Na^+ reabsorption as a result of inhibition of Na^+/K^+ ATPase.

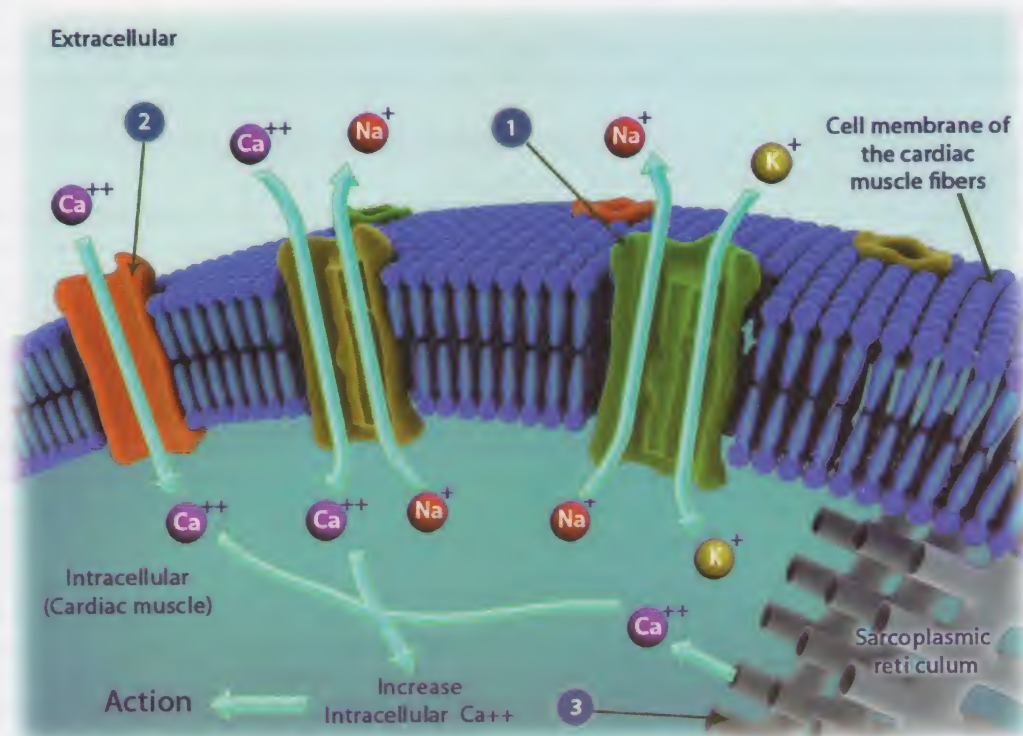


Figure 4-8: The mechanism of action of digitalis

B) Electrical Effects**1- Negative Chronotropic Effect (Indirect Action)**

On SA node; due to

- Increased vagal action by - stimulating central vagal nuclei,
- sensitizing baroreceptors in aortic arch and carotid sinus,
and - sensitizing cholinergic receptors in the heart,
- Anti-adrenergic action as digitalis decreases SA node sensitivity to catecholamines.

2- Negative Dromotropic Effect:**• On AV Node and His-Bundle:**

It decreases conduction velocity and increases the ERP.

In toxic doses; variable degrees of heart block up to complete A-V dissociation may occur due to: its direct and indirect actions i.e., increased vagal activity and anti-adrenergic actions.

• On Atria and Ventricles:

It increases conduction velocity and decreases the ERP especially in low doses.

It decreases conduction velocity and increases ERP especially in high doses.

• On Purkinje Fibers:

Digitalis has an arrhythmogenic action especially in toxic doses resulting in ectopic impulses.

This is due to:

- 1- Activation of voltage-activated and Ca^{++} -activated K^+ channels leading to K^+ efflux which increases automaticity.
- 2- Shifting of the resting membrane potential towards zero.
- 3- Decreasing Na^+ conductance which decreases the slope of phase 0 of the action potential. This decreases the velocity of impulse conduction which increases reentry.
- 4- Decreasing the maximum rate of rise of phase 0 (decreasing V_{max}).
- 5- Decreasing action potential duration.
- 6- Increasing central sympathetic activity in toxic doses resulting in increased automaticity.
- 7- Overload of intracellular Ca^{++} leading to delayed after-depolarization.

N.B.: Effects of Digitalis on Automaticity and Excitability:

- It increases automaticity in the AV node, atria and ventricles due to its direct action.
- It increases excitability in atria and ventricles in low doses and decreases it in high doses.

N.B.: Effect of Digitalis on ECG: (figure 4-9)

- 1- T-wave: its amplitude is decreased (the earliest sign), then becomes isoelectric or inverted.
- 2- ST segment: is depressed (sagging) with upward QRS complex and elevated with downward QRS complex.
- Both ST segment and T wave changes are wrongly interpreted as ischemia.
- 3- PR interval: is prolonged due to delayed A-V conduction.
- 4- QT interval: shortens due to enhanced ventricular repolarization.

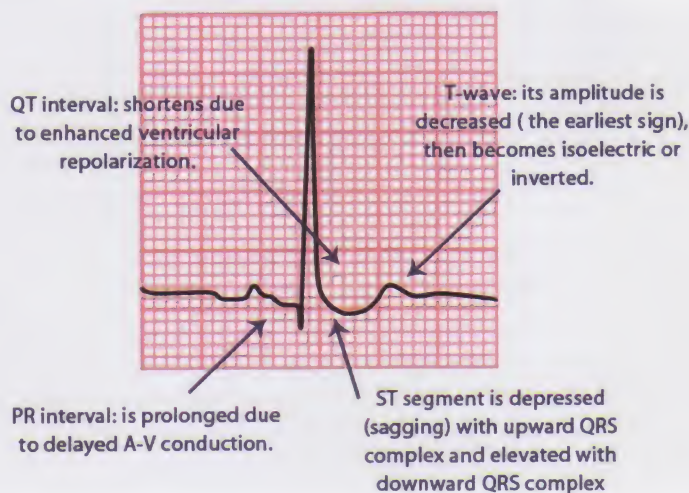


Figure 4-9: ECG changes of digitalis

Therapeutic Uses:

- 1- Atrial fibrillation (AF) with rapid ventricular response (the main indication).
 - It decreases AV conduction and protects the ventricles from the high atrial rates, resulting in improved mechanical ventricular function.
 - It is given before quinidine during conversion of AF to normal rhythm to avoid paradoxical ventricular tachycardia of quinidine, but caution is taken as quinidine increases the plasma level of digitalis and increases digitalis toxicity.
- 2- Atrial flutter: besides the protection of the ventricle as above, digitalis converts atrial flutter into atrial fibrillation then on sudden withdrawal of digitalis, sinus rhythm returns.
- 3- Paroxysmal supraventricular tachycardia.
- 4- Congestive heart failure: but they are now replaced by other new agents.

Contraindications:

- a- Due to its positive inotropic action:
 - High cardiac output failure e.g., thyrotoxicosis.
 - Hypertrophic obstructive cardiomyopathy as it increases outflow obstruction.
- b- Due to its negative chrono- and dromotropic actions:
 - Sinus bradycardia.
 - Heart block (partial or complete).
 - Drug-induced delayed conduction as with β -blockers and calcium channel blockers.
 - Hypersensitive carotid sinus.
- c- Due to its arrhythmogenic action:
 - Arrhythmia of Wolf-Parkinson-White syndrome.
 - Ventricular tachycardia as ventricular fibrillation may occur.
- d- Due to increased incidence of toxicity: These factors increase the sensitivity of the heart to digitalis:
 - Electrolyte disturbances as hypokalemia, hypomagnesemia, and hypercalcemia.
 - Hypothyroidism.
 - Hypoxia and hypercarbia.
 - Recent myocardial infarction.
 - Acute rheumatic carditis.
 - D.C. cardioversion.
 - Renal or hepatic failure (according to the preparation used).

Drug Preparations:

- 1- Digoxin (Lanoxin, Digicap, Cardicap, Cardixin, or Cardioton): 0.25 mg/tab or mL (2 mL-ampoule contains 5 mg). It is taken orally or intravenously.
- 2- Digitoxin: 0.1 mg/tab. It is taken orally.
- 3- Quabain: 0.25 mg/mL. It is taken only intravenously.

Dosage:**1- Slow Digitalization:** (a cumulative method)

- An oral maintenance dose is given daily. It is the safest method.
- Maximum effect is achieved in 4-5 elimination $t_{1/2}$
 - About one week (1.7 day \times 5) for digoxin.
 - About one month (7 days \times 5) for digitoxin.

To speed the onset, the following regimen is chosen:

- 2 tablets/day for a week,
- 2 tablets/12 hours for 2 days,
- or 2 tablets/8 hours for one day, then continue with the maintenance dose.
- Maintenance dose: (1/2 -2 tablets):
 - For digoxin 0.125-0.5 mg/day
 - For digitoxin 0.05-0.2 mg/day.

2- Rapid Digitalization: (a rapid loading method)

- In emergency situations as atrial fibrillation with a rapid ventricular rate or severe acute left ventricular failure: either:

Oral: - Digoxin 0.5 mg/6 hours

or - Digitoxin 0.2 mg/6 hours

then maintain with the daily maintenance dose.

Intravenous: - Digoxin 0.75-1 mg slowly over 10-20 minutes, repeated after 6-12 hours.

Pediatric Doses of Digoxin: • Neonate (up to 1 month): 40-60 μ g/kg.

- Infant (1 month -2 years): 60-80 μ g/kg.
- Children (2-10 years): 40-60 μ g/kg.
- Children above 10-years old: adult doses are given.

Drug Interactions**a- Drugs that Increase Digoxin Level in the Blood:**

- Quinidine, verapamil, and amiodarone as they decrease its renal clearance.
- Tetracycline and erythromycin as they kill gut flora that metabolizes digoxin.

b- Drugs that Decrease Digoxin Level in the Blood:

- Metoclopramide, neomycin, and antacids decrease its absorption.

c- Drugs that Decrease Digitoxin Level in the Blood:

- Phenobarbitone, phenytoin, and rifampicin are enzyme inducers that increase the drug metabolism.

d- Drugs that Increase Toxicity of Digoxin and Digitoxin:

- Sympathomimetics (in addition to hypokalemia, hypomagnesemia, and hypercalcemia).

e- Drugs that Increase the Bradycardia and even Produce Heart Block with Digitalis:

- β blockers
- Calcium channel blockers (verapamil).
- Reserpine
- Succinylcholine.

Digitalis Toxicity

Digitalis has a very low margin of safety.

Therapeutic serum level of digoxin is 0.8-2 ng/mL and toxicity is seen frequently when serum levels exceed 2 ng/mL.

Predisposing Factors:

- Extremes of age.
- See above the contraindications due to increased incidence of toxicity.

Clinical Picture and Side Effects:

- 1- Gastrointestinal effects (early symptoms with mild toxicity): anorexia, diarrhea, nausea, and vomiting.
- 2- Toxic cardiac effects: - Severe sinus bradycardia.
 - Different degrees of heart block.

- Ventricular premature contractions (bigeminy and trigeminy).
- Ventricular tachycardia and ventricular fibrillation.

3- Neurological effects: headache, muscle weakness, drowsiness, disorientation, confusion, and even delirium (digitalis delirium).

4- Ocular effects: blurred impaired white vision (haloes appear on dark objects), impaired color vision, transient amblyopia, diplopia, and retrobulbar neuritis.

5- Gynecomastia and galactorrhea.

6- Skin rash and esinophilia.

7- ECG changes and plasma level should be checked to diagnose toxicity.

Treatment:

1- Digitalis and any potassium-losing diuretics should be stopped.

2- Hospitalization to perform ECG and detect the serum level of digitalis.

3- Potassium (if there is no heart block or renal impairment).

Oral: 2 g/4 hours up to 10 g/day.

Intravenous: 0.5 mmol/min (if serum potassium is < 3.5 mmol/L).

4- Antiarrhythmic drugs: to treat ventricular arrhythmias.

- Phenytoin: it is specific for digitalis induced arrhythmias (supraventricular and ventricular) because
 - it has a sympatholytic action.
 - it antagonizes digitalis effect on conduction.
 - it relieves Na^+/K^+ ATPase inhibition.

Dose: 100 mg i.v. over 5 minutes till arrhythmia disappears.

- Lidocaine: - for ventricular arrhythmias

Dose: 1 mg/kg i.v. followed by 1-5 mg/min infusion.

- Propranolol.

- Verapamil.

5- Atropine to treat the severe bradycardia and heart block. Sometimes, temporary pacing is needed.

6- Immune Fab fragments (digoxin antibodies) (ovine): they bind with digitalis forming a digibind complex which does not produce allergic reactions and is easily eliminated in the urine. It is indicated in life-threatening digoxin toxicity because the drug is very expensive.

N.B.: Digoxin should be stopped for at least 48 hours before elective DC cardioversion; otherwise, ventricular fibrillation may be precipitated. If cardioversion is required, the initial energy level should be low (e.g., 10-25 J) and increased if necessary.

Statins

They are commonly used in elderly patients with ischemic heart.

Action: they reduce cholesterol levels, decrease progression of atherosclerosis and are plaque-stabilizing. They reduce morbidity and mortality in high-risk vascular patients even with the presence of a normal cholesterol level. A statin should be given preoperatively, but the optimal timing is unknown. It has been suggested that statin therapy should be commenced 1 month preoperatively especially in patients with cardiovascular diseases such as coronary artery disease.

Side Effects:

- Hepatic dysfunction.
 - **Statin Myopathic Syndrome:** It causes 4 muscle syndromes which should be assessed preoperatively.
 - 1- **Statin myopathy** (any muscle complaint related to statin therapy).
 - 2- **Myalgia** without elevated creatine kinase (CK).
 - 3- **Myositis** with elevated creatine kinase (CK).
 - 4- **Rhabdomyolysis** with creatine kinase (CK) > 10 times the upper limit of normal + increased s. creatinine with pigmented-induced neuropathy.
- Statins should be continued throughout the perioperative period and liver function tests should be performed preoperatively.

DRUGS ACTING ON THE RESPIRATORY SYSTEM

Respiratory Stimulants

They are either: nonspecific or specific.

A) Nonspecific Respiratory Stimulants

a- Direct Stimulants: they increase synaptic transmission.

- 1- Cortical stimulants: e.g., xanthines, ephedrine, and atropine.
- 2- Brainstem stimulants: e.g., analeptics (they stimulate the respiratory center) such as doxapram, nikethamide (*Coramin*), and ethamivan (*Alertin*).
- 3- Spinal cord stimulants: e.g., strychnine (they block central inhibitory pathways).
- 4- Peripheral stimulants: almitrine.

b- Reflex Stimulants:

For example, ammonia, CO₂, Camphor, and alcohol.

Doxapram (*Dopram*)

It is now the only one used clinically.

Action:

- 1- **At low doses**, it stimulates the **peripheral chemoreceptors** i.e., it mimics low PaO₂ (hypoxia), resulting in an increase in tidal volume and respiratory rate
- 2- **At higher doses**, it also acts as a **nonspecific respiratory stimulant** as it stimulates the depressed medullary respiratory center and awakens patients from deep sleep or anesthesia, but in larger doses it may produce generalized central nervous stimulation and convulsions.
- 3- It has also a sympathomimetic action elevating the blood pressure.

Onset: 1-5 minutes.

Duration: 5-12 minutes.

Pharmacokinetics: it is metabolized in the liver.

Uses:

- 1- **Chronic obstructive airway disease:** these patients are dependent on hypoxic drive. As doxapram mimics hypoxia, it can be used in these patients, but it also increases muscle activity with increasing O₂ consumption and CO₂ production.
- 2- **Drug-induced respiratory and central nervous system depression** such as sedatives, opioids, and anesthetics. In overdosage of opioids, doxapram is better than opioid antagonists as it does not reverse the analgesic action.
- 3- **Recovery from anesthesia.**
- 4- **Prevention of postoperative atelectasis and chest complications.**
- 5- **Facilitation of blind nasal intubation.**
- 6- **Treatment of apnea in premature babies.**

N.B.: For patients with respiratory depression as above, the best treatment is **artificial ventilation** to ensure oxygenation until the respiratory depression is reversed. Respiratory stimulants should be used only as a short term therapy.

Side Effects:

It produces **central nervous system stimulation** resulting in:

- Mental changes such as restlessness, anxiety, agitation, hallucinations, confusion, dizziness, nausea, vomiting, and convulsions.
- Cardiac changes such as tachycardia, arrhythmias, and hypertension.
- Pulmonary changes such as tachypnea, wheezes, coughing and laryngospasm.
- Muscular changes such as rigidity.

Doses:

- I.v. bolus 0.5-1 mg/kg slowly.
- I.v. infusion 1-3 mg/min.

Almitrine

Action:

- It increases the **sensitivity of carotid chemoreceptors** to hypoxemia and hypercarbia.

It does not produce central respiratory stimulation, but it does improve ventilation-perfusion matching by augmenting the hypoxic pulmonary vasoconstrictive reflex.

- Its effect continues for several hours after injection.
- **Interaction between nitric oxide (NO) and almitrine (or phenylephrine) in patients with acute respiratory distress syndrome:** they have an additive action as almitrine or phenylephrine stimulate peripheral chemo-receptors and produce selective pulmonary vasoconstriction especially in non-ventilated alveoli, while inhaled NO causes vasodilatation of the ventilated alveoli. This decreases the shunt and improves the ventilation-perfusion mismatching, correcting the hypoxia in these patients.

Doses:

- I.v. bolus 0.3 µg/kg.

B) Specific Respiratory Stimulants

1- Opioid antagonists such as naloxone.

2- Benzodiazepine antagonists such as flumazenil.

(See before the chapter of "Pharmacology of Anesthesia & Intensive Care").

Drugs Acting on Airway Caliber

They include:

a) **Bronchodilators** as

1- **β agonists:** Epinephrine, ephedrine, isoprenalol. They are rarely used due to their cardiovascular effects. Selective β₂ agonists are now preferred

2- **Anticholinergics:** especially ipratropium bromide.

3- **Magnesium sulphate.**

1, 2, and 3 are discussed above in more details.

4- **Methylxanthines.**

5- **Leukotriene pathway modifiers.**

6- **Other drugs as ketamine, isoflurane, and halothane.**

They are used to treat bronchoconstriction. They are used in isolation or with other measures as oxygen therapy, humidification, antibiotics, physiotherapy, and mechanical ventilation.

b) **Drugs that Prevent Bronchoconstriction (Anti-Inflammatory Drugs)** as

1- **Membrane stabilizers (sodium cromoglycate).**

2- **Steroids.**

These agents are ineffective when bronchoconstriction occurred.

The normal tone of airway smooth muscles is the result of a balance between the opposing effects of sympathetic (mainly β₂) and parasympathetic effects.

Sympathetic (mainly β₂) action stimulates adenylate which in turn changes ATP to cAMP and through kinases, bronchodilatation occurs. Phosphodiesterase enzyme changes cAMP to 5'-AMP so its inhibition causes bronchodilatation.

Para-sympatholytics (cholinergic drugs) stimulate guanylate cyclase which changes GTP to cGMP and through kinases, bronchoconstriction occurs (figure 4-10).

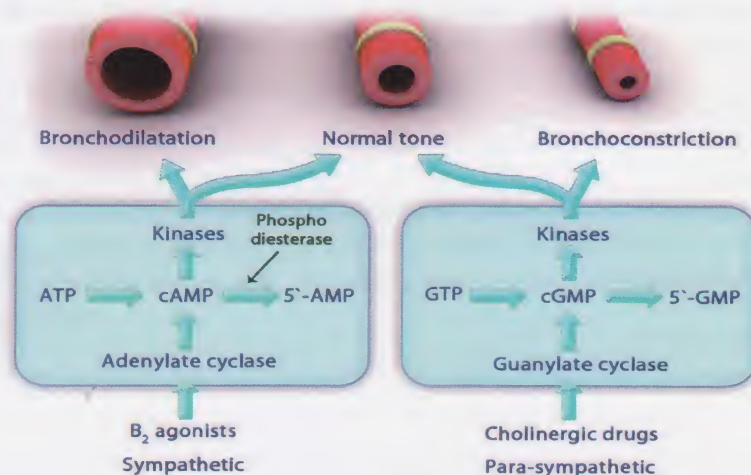


Figure 4-10: The effect of sympathetic and parasympathetic systems on bronchial smooth muscles

Methylxanthines

They are natural alkaloids of plant origin. They are methylated purine bases that are present naturally in coffee, tea, coca, and cola.

Agents:

- 1- Caffeine (a potent central nervous stimulant).
 - 2- Theobromine (coca).
 - 3- Theophylline salts (potent smooth muscle relaxants)
- e.g., - aminophylline (theophylline and ethylene diamine)
- Oxtriphylline (theophylline and choline).
 - Theophylline -Na-glycinate.

Ethylene diamine, choline and Na glycinate increase theophylline solubility.

Mechanism of Action

- 1- They **inhibit phosphodiesterase enzyme** resulting in an increase in cAMP. This leads to:
 - Smooth muscle relaxation which causes bronchodilatation and vasodilatation.
 - Positive inotropic and chronotropic actions.
- 2- They are **adenosine receptor antagonists**, which compete with adenosine at P_1 (A_1) purinoceptors (as adenosine causes bronchospasm and histamine release).
- 3- They **increase circulating catecholamine levels** by:
 - increasing the release of catecholamines from the adrenal medulla.
 - decreasing catecholamine destruction by inhibiting COMT enzyme.
- 4- They **stabilize mast cells and inhibit antigen-induced release of SRS and histamine**.
- 5- They **antagonize the effect of platelet activating factor** (the chemotatic effect).
- 6- They **increase respiratory muscle and diaphragmatic contractions** by mobilization of intracellular calcium.
- 7- They have an **anti-inflammatory action**.
- 8- They act **via prostaglandin inhibition**.
- 9- They **potentiate β_2 agonists**.

Pharmacological Action

They mimic β agonists.

1- Cardiovascular Actions: (especially by theophylline)

- At **low doses**, they inhibit the presynaptic adenosine receptors resulting in an increase in catecholamines which produce **positive inotropic and chronotropic actions** with slight elevation of blood pressure.
- At **therapeutic doses**, they **stimulate the vasomotor center and produce vasodilatation of blood vessels (except cerebral vessels). The resulting effect is no change in blood pressure**
- At high doses, they increase cAMP which increases Ca^{++} influx. This also causes **positive inotropic and chronotropic actions**.

2- Respiratory Actions (especially by theophylline)

- **Bronchodilatation**; therefore, they are used in **bronchial asthma**.

3- Central Nervous Action: (especially by caffeine)

- They stimulate all centers in the brain resulting in:
 - Insomnia, delayed onset of fatigue, tremors, restlessness, irritability up to convulsions
 - **Cerebral vasoconstriction**; therefore, they are used in **headache and migraine**.
 - **Respiratory center stimulation**; so, they are used in **neonatal apnea and chyne-stokes respiration**.
 - Nausea and vomiting.
 - Tolerance.

4- Gastrointestinal Actions: (especially by caffeine)

- At low doses, they increase **gastric acid and pepsin secretion and increase gut motility**.
- At large doses, they cause **gastric irritation and decrease motility** resulting in constipation.

5- Renal Actions: (especially by theophylline)

- They have a **weak diuretic action** due to increased cardiac output and decreased antidiuretic hormone. Therefore, they are used in **congestive heart failure**.

6- Muscular Actions: (especially by caffeine)

- They increase **skeletal muscle contraction** and reverse fatigue most probably by increasing their blood supply and Ca^{++} ions.

- They increase **diaphragmatic contraction** which improves ventilation and decreases hypoxia.
- They relax smooth muscles as ureteric, uterine, intestinal and bronchial muscles.

7- Mast cell Stabilizers.

Pharmacokinetics:

- They are well absorbed orally, but their rectal absorption is slow and erratic.
- They are distributed to all the body and they cross the blood brain barrier and the placenta.
- 90% is metabolized in the liver by xanthine oxidase to active metabolites such as 3-methoxyxanthine. 10% is excreted unchanged by the kidneys.
- Plasma $t_{1/2}$ in a healthy nonsmoker adult is 7-9 hours.

Factors that increase the $t_{1/2}$ (up to 20-30 hours), thus the dose is decreased up to 50% to avoid toxicity:

- 1- Liver dysfunction and cirrhosis.
- 2- Decreased hepatic blood flow e.g., congestive heart failure, β -blockers, and cimetidine.
- 3- Extremes of age (infant and elderly) as they have a slow clearance rate.
- 4- Viral infections and pneumonia.
- 5- High carbohydrate diet.
- 6- Drugs: - Enzyme inhibitors as cimetidine, erythromycin, and chloramphenicol.
 - Oral contraceptive pills.
 - Oral aminophylline (i.e., patients already on aminophylline).

Factors that decrease the $t_{1/2}$ (to 4-5 hours), thus the dose is increased up to 50-100%:

- 1- Smoking (20-40 cigarettes/day) and alcohol intake as they are enzyme inducers.
- 2- Other enzyme inducers as rifampicin, phenobarbitone, phenylbutazone, phenytoin, and carbamazepine.
- 3- Children (1-15 years) as they have a high clearance rate.
- 4- High protein diet and low carbohydrate diet.

Clinical Uses:

a) Theophylline:

- 1- It is the **second line of treatment of bronchial asthma** while β_2 -agonists are the first line.
- 2- It decreases symptoms of chronic obstructive airway disease.
- 3- Acute left ventricular failure and pulmonary edema.
- 4- Congestive heart failure.
- 5- As a spasmolytic agent in biliary, intestinal, ureteric colic and dysmenorrhea spasms.
- 6- In the intensive care, it improves exercise tolerance in intensive care patients who are on a weaning programme.

b) Caffeine:

- 1- With ergot alkaloids in treatment of headache and migraine.
- 2- As a nonspecific respiratory stimulant.

Side Effects:

They have a very narrow safety margin (i.e., a very low therapeutic index).

Their therapeutic range is 5-15 (up to 20) mg/L or $\mu\text{g/mL}$.

Adverse effects depend on:

a) The plasma concentration:

- **At serum level 15 mg/L:**
 - Gastrointestinal effects as nausea, vomiting, diarrhea, reactivation of peptic ulcer and abdominal discomfort.
 - Cardiovascular effects: palpitation (tachycardia) and headache.
- **At serum level 20 mg/L:**
 - Central nervous stimulation as irritability and restlessness.
 - More cardiovascular effects as hypotension and arrhythmias.
- **At serum level > 40 mg/L:**
 - More central nervous system effects as headache, up to convulsions.
 - More cardiovascular effects as severe hypotension and cardiac arrest.

b) The route of administration:

- **Rapid i.v. injection** causes high peak plasma concentration which increases the side effects especially hypotension, arrhythmias, syncope, and death.
- **Oral intake** causes gastritis and peptic ulcers.

- Repeated rectal intake causes proctitis.
- c) **Prolonged usage:** causes habituation, constipation, and tolerance.
- d) **The agent used:**

Theophylline crosses the blood brain barrier and produces more central nervous stimulation and insomnia.

Drug Interactions

- Enzyme inhibitors and enzyme inducers as above.
- With epinephrine, other β agonists, and excess coffee and tea; there are increased cardiovascular side effects as arrhythmias.
- With ephedrine, there are increased central nervous side effects such as insomnia.
- Corticosteroids in the same infusion fluid decrease the action.

Doses and Preparations

1- Theophylline Salts:

a) **Aminophylline dihydrate** (theophylline and ethylene diamine).

1- Oral route: (Minophylline)

- Loading dose 7.6 mg/kg.
 - Maintenance dose (1/2 of the loading dose) 3.8 mg/kg/8hours for nonsmoker adults.
- It is taken every 6 hours by smoker adults and children.

2- Oral sustained release preparations: (Quibron-T SR, Theofar SR, Theo-Dur, or Theo-SR)

- For adults: 225-450 mg/12 hours.
- For children: 6-12 mg/kg/12 hours.

3- Intravenous route: (Minophylline)

- Loading dose 5 mg/kg slowly over 15-20 min.
- Maintenance dose (1/10 of the loading dose) 0.5 mg/kg/h i.v. infusion.

If the patient is already taking theophylline, half the loading dose should be given and the plasma concentration should be checked frequently.

4- Rectal suppository: (Amriphylline, or Minophylline)

b) **Oxtriphylline** (choline theophylline): 200-400 mg oral or rectal.

2- Theophylline Variants:

- Acephylline (with phenobarbitone in *Epicophylline* or *Etaphylline*)
- Diprophylline.
- Oxpentifylline.
- Enprophylline.
- Etamiphylline.
- Proxyphylline.

Precautions:

- 1- The **dose should be decreased** in patients with liver dysfunction...etc (see above factors that increase the plasma $t_{1/2}$) and should be **increased** in smokers ...etc (see above factors that decrease the plasma $t_{1/2}$).
- 2- **Oral doses** should be **taken with meals** to avoid gastrointestinal irritation and should be avoided in patients with peptic ulcers.
- 3- **I.v. doses** should be taken **slowly and not in a central venous catheter** as this increases its cardiotoxicity.
- 4- **Careful patient monitoring** and observation for signs of toxicity are mandatory. **Measuring the serum level** is preferred especially in the first 24 hours.
- 5- Aminophylline is a strong alkaline solution and should **never be given intramuscularly or subcutaneously**.

Leukotriene Pathway Modifiers

They include: **Monotelukast** (*Singulair*), **Zafirlukast** (*Accolate*), and **Zileuton** (*Zyflo*).

Mechanism of Action:

Leukotrienes arise from leukocytes and stimulate airway smooth muscle contraction by a non-histamine mechanism. Leukotrienes and other products of the 5-lipo-oxygenase pathway induce pathophysiological responses similar to those associated with asthma-edema, migration of eosinophils, and stimulation of airway secretions. The leukotrienes modifiers are particularly useful in two types of bronchial asthma:

- **Exercise-induced asthma** (especially for children who want to exercise at school without having to use an intermediate acting inhaled β_2 agonists)
- **Aspirin-induced asthma.**

Anti-Inflammatory Drugs

1- Membrane Stabilizers

They include disodium cromoglycate (Cromolyn Na), ketotifen, and nedocromil Na.

Disodium Cromoglycate

It is a derivative of khellin, an Egyptian herbal remedy.

Mechanism of Action:

It **stabilizes the mast cell membrane** (and may interact with other inflammatory cells as macrophages and eosinophils) preventing degranulation and release of allergic mediators especially SRS-A. This occurs by:

- Closing Ca^{++} channels and preventing antigen-induced increase in Ca^{++} permeability which decreases Ca^{++} influx.
- Inhibition of phosphodiesterase enzyme, increasing cAMP which inactivates the contractile micro-filamentary protein needed for degranulation of mast cells.

Uses:

1- **Prophylaxis in between bronchial asthma attacks.** It is the first line in **children** because steroids cause growth retardation. It is not used as a bronchodilator during the attack.

2- Treatment of allergic rhinitis, hay fever, allergic conjunctivitis, ulcerative colitis, and Crohn's disease.

Side Effects:

Direct irritation results in bronchospasm, nasal congestion, cough, pharyngeal irritation, laryngeal irritation, urticaria, pneumonitis, and stinging sensation of the eyes.

Doses: Cromolyn Na (Intal)

1- Inhalation by spinhaler: 20 mg capsules (contains powder)/4-6 hours.

2- Nebulizer: 10 mg/mL solution.

3- Metered aerosol: 1 mg/puff.

Ketotifen (Zaditen)

It is similar to disodium cromoglycate but,

- it also has an antihistaminic action so it produces drowsiness and sedation
- it has an anticholinergic action, so it produces dry mouth
- it has a longer duration of action (12 hours)
- it is taken orally as 1 mg tablet or capsule/12 hours.

Nedocromil Na (Tilade)

It is similar to disodium cromoglycate but,

- it has a longer duration of action (12 hours)
- it is taken by aerosol 4 mg/12hours
- it is not irritant.

2- Steroids (Glucocorticoids)

Steroids are discussed here as regard their pulmonary actions and other actions.

Mechanism of Action	Uses and Side Effects
1- Anti-inflammatory action: <ul style="list-style-type: none"> • They prevent migration of phagocytic cells at the site of inflammation and decrease their ability to phagocytosis. • They stabilize lysosomal membranes and so decrease proteolytic enzymes at site of inflammation. • They stimulate synthesis of a protein called lipocortin, via acting on intracellular steroid receptors, which inhibit the activity of phospholipase A_2. This inhibits formation of arachidonic acid from mast cell membrane phospholipids resulting in decreased prostaglandins, platelet activating factors, leukotriene production i.e., they stabilize the mast cell membrane. • They inhibit endothelial proliferation, which decreases healing and also decreases fibrosis. • They inhibit cytokine production which initiates the inflammatory reactions. 	Uses: <p>In pulmonary system:</p> <ul style="list-style-type: none"> • Bronchial asthma: <ul style="list-style-type: none"> ◦ Chronic bronchial asthma not responding to other treatment (by the oral route). ◦ Prophylactic in between attacks (by the oral route). ◦ Acute severe asthma (by the inhalational route). ◦ Status asthmaticus (by the i.v. route). ◦ Morning tightness. ◦ Treatment of tolerance induced by β_2 agonists. • Chronic obstructive airway diseases. • Sarcoidosis. • Interstitial lung disease. • Pulmonary eosinophilia. <p>In other systems:</p> <ul style="list-style-type: none"> • Optic neuritis. • Ulcerative colitis.

<p>2- Immunosuppressive action:</p> <ul style="list-style-type: none"> • They decrease the number of circulating T lymphocytes, eosinophils, and macrophages. • They decrease proliferative response of lymphocytes to antigen. • They inhibit the processing of antigen by macrophages. • They inhibit antibody production by B-lymphocytes. • They inhibit the effect of lymphokines (e.g. interferon). 	<ul style="list-style-type: none"> • Dermatitis. • Allergic reaction and anaphylactic shock. • Organ transplantation. • Autoimmune diseases as rheumatoid arthritis, systemic lupus, arthritis as osteoarthritis, nephrotic syndrome, hemolytic anemias, myasthenia gravis, and rheumatic myocarditis. <p>Side effects:</p> <ul style="list-style-type: none"> • Increased susceptibility to infections such as oropharyngeal candidiasis with dysphonia, throat irritation and cough (by the inhalational route). • Delayed wound healing.
<p>3- Metabolic action:</p> <ul style="list-style-type: none"> • They increase blood glucose level by: <ul style="list-style-type: none"> ▫ decreasing peripheral glucose utilization (i.e. anti-insulin). ▫ increasing gluconeogenesis (i.e. catabolic effect). ▫ increasing glycogen storage (i.e. glycogenesis). • They produce protein catabolism. • They increase lipolysis and produce fat redistribution. • They increase sodium and water retention by: <ul style="list-style-type: none"> ▫ its weak mineralocorticoid action resulting in increasing sodium and water reabsorption and increasing potassium and hydrogen secretion. • They decrease calcium in the blood and bone. 	<p>Side effects:</p> <ul style="list-style-type: none"> • Diabetes mellitus. • Muscle wasting. • Weight gain and fat deposition in the face (moon face) and trunk (buffalo hump). • Hypokalemia. • Metabolic alkalosis. • Growth retardation in children and osteoporosis in adults.
<p>4- Action on catecholamines:</p> <ul style="list-style-type: none"> • They stimulate adenylate cyclase enzyme increasing cAMP as catecholamines. • They stimulate N-methyltransferase resulting in increased methylation of noradrenaline. • They block catecholamine reuptake and potentiate their action. • They increase sensitivity of B₂-adrenoceptors and therefore augment the effect of agonists together with increasing receptor density and prevention of tachyphylaxis. 	<p>Side effects:</p> <ul style="list-style-type: none"> • Hypertension. • Glaucoma.
<p>5- Other actions:</p> <ul style="list-style-type: none"> • Exogenous steroids has the same actions as endogenous steroids • They decrease capillary permeability resulting in decreased mucosal swelling. • They decrease mucus production. • They increase HCl secretion in the stomach. • They stimulate renin angiotensin system. • They are essential for surfactant production. • They change mood and behavior. • On chronic use, they decrease bronchial reactivity. <p>They have no direct bronchodilator effect.</p>	<p>Uses:</p> <ul style="list-style-type: none"> • Replacement therapy in chronic and acute adrenal insufficiency (Addisonian crisis). • Dexamethasone suppression test to diagnose Cushing syndrome. • Cerebral edema especially around tumors by dexamethasone. • Infant respiratory distress syndrome. <p>Side effects:</p> <ul style="list-style-type: none"> • Acute adrenal insufficiency on sudden withdrawal after its chronic use. • Hypothalamic pituitary suppression if ACTH is used. • Iatrogenic Cushing syndrome. • Precipitation of peptic ulcer. • Depression, psychosis, and insomnia. • Increased appetite and weight gain.

Preparations Used in Bronchial Asthma

a) Inhalational Steroids: it is the best route due to minimal systemic effects, minimal adrenal suppression and maximal pulmonary effects.

- Beclomethasone: 400-500 µg/day.
- Betamethasone dipropionate (*Becotide* or *Clenil forte*) (with salbutamol *Clenil compound*).
- Triamcinolone (*Azmacort*)
- Fluticasone propionate (*Flixotide*) (with salmeterol *Seretide*)

The dose is 50-100 mg/6 hours (1-2 puffs).

b) Oral Steroids:

- Intermediate acting: prednisolone (5 mg/tablet): 40-100 mg/day then the dose is decreased gradually to 10-15 mg/day.
- Long acting: dexamethasone and betamethasone: 0.5-1 mg/6hours.

c) Parenteral Steroids (i.v. Route):

- Hydrocortisone Na hemi-succinate: 3-4 mg/kg/6 hours.
- Dexamethasone (a 2 mL ampoule contains 8 mg).
- ACTH is used especially in asthmatic children because it is less liable to produce growth retardation and does not produce adrenal suppression.

The dose is given as - a slow release preparation 0.25-2 mg twice a week.
or - 20-30 IU/day i.v.

Precautions

- 1- In switching patients from oral to inhaled glucocorticoid therapy, oral therapy should be tapered gradually to avoid adrenal insufficiency.
- 2- If glucocorticoids are used in mild attacks, they should be given by inhalation to avoid severe adverse effects.
- 3- To prevent candidiasis, the patient should gargle water and spit after each inhaled steroid.

Drugs Acting on Pulmonary Vessels

There are many drugs and factors that increase or decrease pulmonary vascular resistance.

Factors increasing pulmonary vascular resistance i.e., vasoconstriction	Factors decreasing pulmonary vascular resistance i.e., vasodilatation
<ul style="list-style-type: none"> • Hypoxia • Acidosis. • α-Adrenergic agonists. • β-Adrenergic antagonists. • Angiotensin II • Histamine. • Serotonin. • Non-steroidal anti-inflammatory drugs as indomethacin or aspirin as they inhibit PGI₂ production. • Thromboxane. • Protamine. 	<ul style="list-style-type: none"> • Oxygen administration. • Alkalosis. • α-Adrenergic antagonists. • β-Adrenergic agonists. • ACE inhibitors. • Acetylcholine. • Prostaglandins (PGs) PGI₂ and PGD₂. • Calcium channel blockers. • Aminophylline. • Nitrates and nitrites. • Nitric oxide • Sodium nitroprusside • Hydralazine. • Diazoxide. • Tolazoline.

N.B.: Hypoxia, hypercarbia, histamine release, and acidosis cause vasodilatation in all blood vessels except pulmonary vessels in which they cause vasoconstriction.

Uses:**a) Decreasing pulmonary vascular resistance, indicated in:**

- Primary pulmonary hypertension.
- Some congenital heart diseases as right to left shunt e.g., Fallot's tetralogy.
- Mitral valve disease.
- Chronic obstructive airway disease and cor pulmonale.
- Acute respiratory distress syndrome.
- Acute respiratory failure.
- Acute pulmonary edema.

b) Increasing pulmonary vascular resistance, indicated in:

- Some congenital heart diseases as left to right shunts e.g., ventricular septal defect.

Nitric Oxide (NO)

It was previously called endothelium-derived relaxing factor (EDRF).
It was discovered in 1987.

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Nitric Oxide (NO)

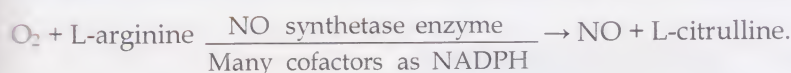
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Nitric Oxide (NO) Molecule

- It is a small uncharged molecule and highly lipid soluble; so, it can cross the cell membrane freely.
 - It has an unpaired electron; so, it acts as a free radical.
 - It is a colorless, nearly odorless gas normally found in the atmosphere in the range of 10-5600 part per billion (ppb).
 - It interacts:
 - a- In the gaseous phase, with O₂ (or air), producing nitrogen dioxide (NO₂) which is a reactive toxic metabolite causing pulmonary edema.
 - b- In the aqueous solution, with superoxide radical (O₂[•]), producing per-oxy-nitrite (OONO[•]) which is a highly toxic oxidant.
 - c- It binds rapidly to iron in the heme moiety of proteins such as hemoglobin (Hb), soluble guanylyl cyclase enzymes, and enzymes of the electron transport chain.
 - d- It binds rapidly to Hb producing nitrosyl-hemoglobin (NOHb) and met-Hb (both Hb and NO inactivate each other).
- N.B.: N₂O = Nitrous oxide.
 NO = Nitric oxide.
 NO₂ = Nitrogen dioxide.
 N = Nitrogen.

Endogenous NO synthesis

- It is formed in a 5 electron oxidation reaction in which:



O₂ combines with the terminal guanidinium nitrogen of L-arginine.

Three types of nitric oxide synthetase enzymes (NOS) are present:

1. Neuronal NOS (nNOS) (NOS-isoform I) on chromosome 12. It is constitutive NOS.
2. Endothelial NOS (eNOS) (NOS-isoform III) on chromosome 7. It is constitutive NOS.
3. Immunological (iNOS) (NOS-isoform II) on chromosome 17. It is inducible NOS.

Constitutive NOS	Inducible NOS
<p>It includes : nNOS and eNOS</p> <p>It is present in:</p> <ul style="list-style-type: none"> - Endothelial cells. - Neurons. - Peri-vascular nerve fibers. - Adrenal medulla. - Macula densa of the kidney. 	<p>It includes: iNOS</p> <p>It is present in:</p> <ul style="list-style-type: none"> - Macrophages. - Hepatocytes. - Vascular smooth muscles. <p>It is usually not present under basal conditions.</p>
<p>Activation: It is activated by shear forces. It requires an increase in intracellular Ca⁺⁺ for its activation as intracellular Ca⁺⁺ binds to calmodulin producing Ca⁺⁺- calmodulin complex which activates constitutional NOS i.e., Ca⁺⁺ dependant enzyme. It produces small amounts of NO (picomoles).</p>	<p>Activation: It requires stimuli as endotoxins (lipopolysaccharide) and cytokines. This causes transcription of inducible NOS gene increasing inducible NOS (it does not require intracellular Ca⁺⁺). It produces large amounts of NO (nanomoles).</p>

N.B.: L-arginine analogues (e.g., N-mono-methyl L-arginine) cause competitive inhibition of NOS enzyme.

Physiological Effects of Endogenous NO:

1- Cardiovascular Effects:

a- It produces **vasodilatation of the blood vessels all over the body.**

- It regulates systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), cardiac output, and coronary and cerebral circulations.

For example, it mediates the effect of CO₂ on cerebral blood flow (CBF) as it causes cerebral vasodilatation which increases CBF without altering cerebral auto-regulation.

- So, - Its decreased production causes vasospasm which in turn causes systemic hypertension, pulmonary hypertension, angina and erectile dysfunction.

- Its increased production causes excessive vasodilatation which in turn causes septic shock, and neuronal toxicity after ischemia.
- It modulates ischemic/reperfusion injury (e.g., transplantation) of the heart, lung, kidney and liver.
- NO may protect against injury by:
 - improving blood flow
 - decreasing neutrophil activation and adhesion to endothelial cells
 - scavenging of oxygen derived free radicals
 - termination of self-sustained lipid peroxidation reaction.
- NO may promote injury by:
 - production of peroxynitrite which is a powerful oxidant
 - release of iron from its storage site.

Molecular Mechanism of Vasodilatation:

- NO production is increased by - physiologic stimuli such as blood flow, shear stress, hypoxia and hypercarbia.
 - pharmacological stimuli: serotonin, and histamine.
 - The mechanism of action of NO is discussed in figure 4-11.
- N.B.: Vasodilatation induced by nitro-dilators as nitroglycerine, sodium nitroprusside, and hydralazine is believed to be due to increased NO production.
- b. It produces **negative inotropic** and **negative chronotropic** effects.

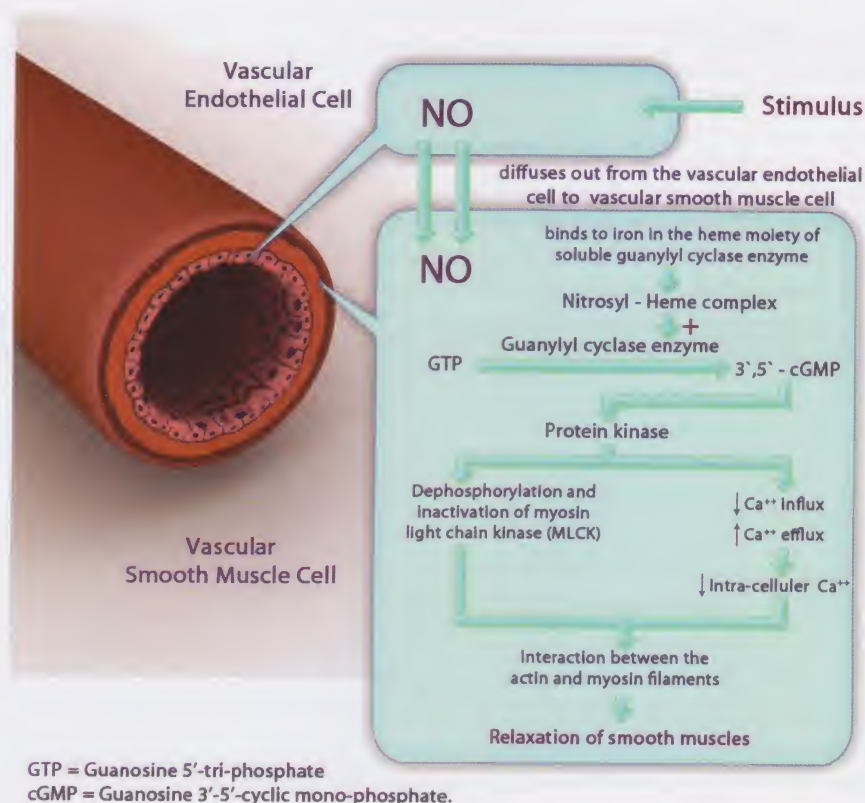


Figure 4-11: Molecular mechanism of NO

2. Neurological Effects:

It may act as a **neurotransmitter** in the brain, spinal cord and peripheral nervous system.

In the brain:

- It may play a role in long-term potentiation in the hippocampus and long-term depression in the cerebellum.
- It may be responsible for glutamate neurotoxicity after cerebral ischemia (NMDA receptors activation by glutamate causing NO release).
- It regulates hormone release in the hypothalamo-pituitary axis.

- In nNOS knock out (deficient) mice, there is a significant decrease in the infarct size after focal cerebral ischemia compared to wild-type mice. In contrast, in eNOS knock out mice, there is a significant increase in the infarct size so, in the future, designing drugs that selectively stimulate eNOS and inhibit nNOS will increase ischemic tolerance of neuronal tissues.

- It is the neurotransmitter in non-adrenergic, non-cholinergic neurons which innervate:
 - Mesenteric plexus causing smooth muscle relaxation of the gastrointestinal tract.
 - Corpora cavernosa and adventitia of penile tissues.
 - Smooth muscles of the airway causing bronchodilatation.

3. Effects on Platelets:

- It decreases platelet (and neutrophil) aggregation and adhesion (i.e., synergistic action to prostacyclin).

4. Immunological (Cytotoxic) Effects:

- It causes damage to bacteria, fungi, protozoa and tumor cells.
- It also causes - DNA trauma or damage.
 - Tissue damage by peroxynitrite, hydroxyl radicals and nitrogen dioxide.
 - Inhibition of mitochondrial enzymes.
- It may play a role in transplant rejection.

5. Inflammatory Modulating Effect:

- It decreases leukocyte adhesion to endothelial cells.
- It alters cytokine release.

NO Half Life:

It has an ultra-short effective half life **0.5-1 sec** due to its rapid oxidation to nitrites and nitrates and its antagonism by substances such as Hb.

NO and Anesthesia:

1. Anti-nociception:

NO has an anti-nociceptive action. Cholinergic stimuli activate the neuronal NOS enzyme which increases NO production. This may explain the analgesic effect of

- Intrathecal neostigmine.
- Intrathecal and epidural clonidine.

2. Inhalational Anesthetics:

They inhibit NO production by the vascular endothelium.
NO increases the MAC of inhalational anesthetics.

Inhaled NO

Action:

Selective pulmonary vasodilator action:

NO has 2 types of selectivity:

- **Dose independent selectivity** i.e., selective to pulmonary > systemic vessels.
- **Dose dependent selectivity** (it is lost in high doses) i.e., it is distributed to the well ventilated alveoli > non-ventilated alveoli, then it diffuses to the adjacent pulmonary vascular bed causing relaxation of vascular smooth muscles and producing selective pulmonary vasodilatation. This action results in:
 - **Decreased intrapulmonary shunt** with maintaining **ventilation/perfusion matching**. This improves arterial hypoxemia.
 - **Decreased pulmonary vascular resistance** with **decreasing pulmonary hypertension**.
 - **Reduced right ventricular wall stress**.
 - Increased coronary artery blood flow.
 - Reduced need for inotropic support.
 - Increased right and left ventricular outputs.

Advantages: It has no systemic effects because any amount diffusing to the blood is rapidly inactivated by Hb.

Therapeutic Uses:

1. Acute Respiratory Distress Syndrome (ARDS):

- In ARDS, there are 2 main pathological features: - arterial hypoxemia.
and - pulmonary hypertension.

NO causes a selective pulmonary vasodilator action, as above, therefore;

- **Arterial hypoxemia is improved:**

It is short-lived, for 1-2 days.

It has an additive action with other methods e.g. prone position ventilation.

- **Pulmonary hypertension is improved:** which improves right ventricular performance and pulmonary edema.

Both improvement of hypoxemia and pulmonary hypertension lead to enhanced lung healing.

- It also produces bronchodilatation.
- NO does **not produce the side effects of other nonselective pulmonary vasodilators** as nitroglycerine, sodium nitroprusside, nifedipine, PGI₂, and PGE₂. These nonselective agents cause:
 - Systemic hypotension.
 - Vasodilatation of the pulmonary vascular bed of the poorly ventilated alveoli with inhibition of hypoxic pulmonary vasoconstriction, decreasing ventilation/perfusion matching and increasing intrapulmonary shunting. This worsens arterial hypoxemia.
- Inhaled NO should be **continuously** administrated to produce its effect. Discontinuing NO for even short periods e.g., during transporting ARDS patients to the operating room causes rebound pulmonary hypertension. This causes acute hypoxemia or right ventricular failure. Therefore, NO should be administrated also during patient's transport and during anesthesia inside the operating room.
- Interaction between NO and other ARDS therapies:
 - a. **NO with almitrine (or phenylephrine):** Have an additive action as almitrine or phenylephrine stimulates peripheral chemo-receptors producing selective pulmonary vasoconstriction which causes vasoconstriction of non-ventilated alveoli. Therefore, improvement of the shunt occurs.
 - b. **NO with permissive hypercapnia:** NO improves oxygenation during normo- and hypercapnic ventilation.

2. Pulmonary Hypertension:

For example:

- Primary pulmonary hypertension.
- Secondary pulmonary hypertension.
- Persistent pulmonary hypertension of the newborn; the disease is characterized by pulmonary hypertension, anatomical right to left shunt (patent foramen ovale and patent ductus arteriosus) and respiratory distress syndrome due to meconium aspiration or sepsis. This is the only indication approved by the US Food and Drug Administration (2003).
- Acute right heart syndrome; in which pulmonary hypertension causes right ventricular failure, and in severe cases, paradoxical inter-ventricular septal shift occurs causing left ventricular failure, therefore; inhaled NO improves cardiac output, stroke volume and mixed venous oxygenation.

3. Chronic Pulmonary Disease:

a. COPD, chronic asthma, pulmonary fibrosis, and respiratory failure:

NO produces selective pulmonary vasodilatation and bronchodilatation. This improves arterial hypoxemia.

b. Pulmonary edema of high altitudes:

It has elements of pulmonary hypertension and increased alveolo-capillary membrane permeability.

4. Perioperative Management in Cardiac Surgery:

- Pulmonary hypertension occurring after mitral valve surgery.
- Surgery for congenital heart disease and pulmonary hypertension.
- Pulmonary hypertension occurring after cardio-pulmonary bypass: pulmonary hypertension occurs due to endothelial dysfunction or protamine sulfate reaction.
- Cardiac transplantation: It is given preoperatively to determine the presence of reversible pulmonary hypertension in patients scheduled for cardiac transplantation because irreversible pulmonary hypertension contraindicates cardiac transplantation. It is safe because there is no systemic vasodilatation. It is also given postoperatively to treat right ventricular failure occurring after cardiac transplantation.

5. Perioperative Management in Lung Surgery:

- During one lung ventilation.
- During lung transplantation. The same effects are as above.

6. Perioperative Management in Organ Transplantation:

For example, in lung, liver, kidney, and heart transplantations; NO decreases ischemic/reperfusion injury (see above).

7. Congenital Diaphragmatic Hernia:

It is characterized by: - Potentially reversible pulmonary hypertension.

- Arterial hypoxemia.

- Systemic hypotension.

So, NO may be used in selected babies to avoid use of extracorporeal membrane oxygenation.

8. Sickle Cell Disease:

- NO decreases sickling.
- NO treats acute chest syndrome.
- NO decreases pain associated with vaso-occlusive crisis.

9. Other Effects:

- NO inhibits leukocyte infiltration and inflammation.
- NO inhibits superoxide production and scavenges O₂ free radicals; therefore, it decreases O₂ toxicity as it attenuates vascular damage and smooth muscle proliferation.

Dose:

- 40-80 part per million (ppm). In ARDS, it is used continuously over 1-3 weeks.

Side Effects:

1. Met-hemoglobinemia.

2. Platelet dysfunction:

NO decreases platelet aggregation and adhesion, so it prolongs the bleeding time.

3. Formation of toxic metabolites such as:

- Nitrogen dioxide (NO₂), when it reacts with O₂ or air. NO₂ may cause pulmonary edema and alveolar hemorrhage.
- Peroxynitrite (OONO•), when it reacts with superoxide radicals. It is very toxic.
- Toxic metabolite (ONOOOCO₂), when it reacts with CO₂ in patients with hypercarbia. It causes direct or indirect tissue toxicity.

4. Rebound phenomenon:

It occurs on sudden discontinuation of inhaled NO where pulmonary hypertension occurs more than the baseline levels. Arterial hypoxemia and right ventricular failure occur due to suppression of endogenous NO production (i.e., feed-back inhibition); therefore, patients should be:

- weaned off inhaled NO gradually,
- closely observed continuously, even after NO discontinuation.

Phosphodiesterase inhibitors as dipyridamole prevent this rebound phenomenon.

5. Mutagenicity.

6. Delaying lung repair and recovery: because NO redistributes the blood flow away from the damaged hypoxic region.

7. Hemodynamic instability:

- In patients with pre-existing severe left ventricular dysfunction, NO improves right ventricular function due to pulmonary vasodilatation causing a small increase in left ventricular volume which in turn increases left ventricular end diastolic pressure (LVEDP) and pulmonary edema.

Inhaled NO Cylinders

- Color: - The body is silver in color, painted with a label carrying a notice "Toxic Gas".
- The shoulder is amber yellow.
- Storage: NO is stored in nitrogen (N₂) (If it is stored in O₂, it will be converted into higher toxic oxides).
- Concentration should be limited to 1000 ppm to avoid over-dosage.

Delivery System of NO

• NO delivery is still developing; there are 3 **technical difficulties** which arise on configuring a system for administering NO in the operating room:

1. Inability to maintain accurate and stable NO concentration because NO dose is affected with changes in the FiO₂ and ventilatory pattern.
2. Formation of nitrogen dioxide (NO₂) by the reaction of NO with O₂ or air, which is toxic causing increased airway reactivity and pulmonary edema.
3. Inadequate monitoring systems for the levels of NO and NO₂.

• **Monitoring** should be done at a **site at least 30 cm from the site of NO introduction** because the viscosity differences between NO and air delay complete mixing.

N.B.: Monitoring of met-Hb level in the blood should also be done.

Methods of NO Administration

1- During Manual Ventilation: NO is mixed with O₂ and introduced into the gas inlet port (figure 4-12), but this system has the following disadvantages:

Figure 4-12: Manual ventilation with O_2 and NO

- 1- NO concentration is changed with changes in O_2 flow, minute ventilation or NO gas flow.
- 2- This system should be flushed between uses to avoid buildup of NO_2 resulting from residual NO coming into contact with O_2 .

2- During Mechanical Ventilation by Anesthesia Ventilators:

- a- NO is introduced into the inspiratory limb of the ventilatory circuit (figure 4-13).

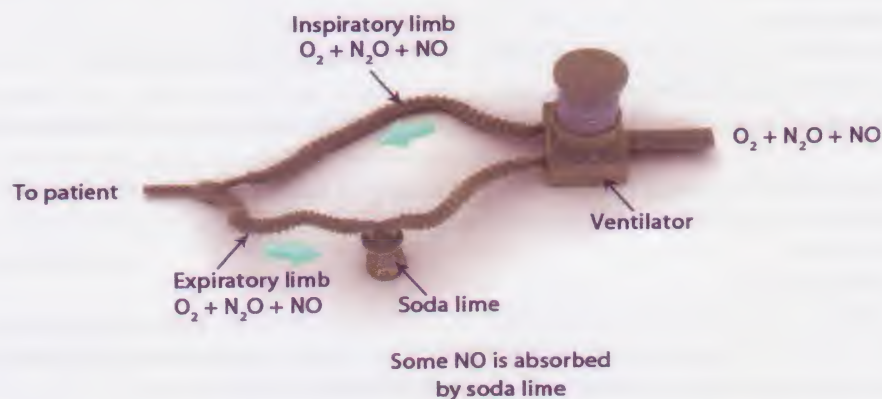


Figure 4-13: NO and mechanical ventilation

Disadvantages: It gives unpredictable NO concentration because:

- Soda lime absorbs both NO and NO_2 in variable amounts.
- NO is mixed with rebreathing gas containing variable amounts of NO.

- b- NO is introduced using a nitrous oxide (N_2O) flowmeter.

Disadvantages:

- The densities of NO and N_2O are different which make the N_2O flowmeter inaccurate in delivering NO, but if the fresh gas flow exceeds the minute ventilation, stable NO concentration occurs.

3- During Mechanical Ventilation by Intensive Care Ventilators:

Disadvantages: There should be a scavenging system for the exhaled gases because in intensive care ventilators, there should be no rebreathing of exhaled gases.

There is no system commercially available for NO delivery, but recently I-NOVent (Ohmeda) is commercially available as a delivery and monitoring system with the following advantages:

- It provides a constant NO concentration independent of ventilatory pattern.
- It provides minimal NO_2 formation.
- It provides good monitoring system.

Drugs Acting on Mucociliary Function

Physiological Considerations:

Mucociliary function consists of

- 1- **The mucus blanket:** that is formed of two layers:

- A high-viscosity mucopolysaccharide gel, secreted by the goblet cells. It is stimulated by irritant factors.
- A low-viscosity serous layer (deeper to the mucopolysaccharide layer), secreted by bronchial glands. It is under control of vagal nerve, in addition to the local factors.

- 2- **Ciliary motility:**

Cilia are normally propelling the outer blanket of mucus (with entrapped dust, soot or microorganisms) over the serous layer in a direction from the peripheral airways to central airways to be expectorated.

Factors Affecting the Mucociliary Function:

Factors depressing mucociliary function	Factors optimizing mucociliary function
<ul style="list-style-type: none"> • Extremes of temperature. • Dehydration. • Smoking and dry gases. • Acidic environment. • Drugs: - Alcohol. - Atropine. - Anesthetics. - Opioids. 	<ul style="list-style-type: none"> • Temperature range 29-34 °C. • Hydration. • Humidification. • Drugs: - Sympathomimetics. - Methylxanthines.

Drugs Improving Mucokinetics: are either hydrating agents or mucolytics.

Respiratory secretions are formed of two layers:

- A hydrophilic (water soluble) layer: It faces inward and contacts the epithelium. It keeps the mucosal surface moist.
- A hydrophobic (water insoluble) layer: It faces outward, towards the lumen of the airways. It is composed of a meshwork of muco-protein stands (called mucus threads) hold together by disulfide bridges. It traps particles and debris in the airways.

Hydrating Agents

1- Systemic hydration.

2- Aerosolized water or hypotonic saline are good for hydration, but

- Aerosolized normal saline may provoke bronchospasm.
- Aerosolized hypertonic saline is used to induce irritation to stimulate ciliary clearance.

Methods of hydration are discussed in the chapter of "Basic Physics for Anesthesia & Intensive Care".

Mucolytics

They are used for productive cough as they liquefy viscid bronchial secretions.

1- Bromohexine (*Bisolvon*): it fragments the mucopolysaccharide fibril structure of mucus.

Ambroxol (*Ambroxol*, *Bronchopront*, or *Mucofar*) (*Trisolvin* with theophylline) is a metabolite of bromohexine.

2- Cysteine derivatives as N-acetylcysteine (*ACC 200*, *Acetylcistein*, *Mucomyst*, or *Mucosolvan*), methyleysteine and carboxymethyl cysteine (*Mucosol* or *Solvex*):

They split disulfide bonds between muco-protein strands in the mucus (sputum).

They are taken either systematically or by inhalation, but they cause irritation to the airway resulting in bronchospasm especially in asthmatic patients.

3- Detergents e.g., tyloxapol aerosol.

4- Potassium iodide.

Expectorants

They are used for productive cough as they facilitate removal of bronchial secretions.

1- Potassium iodide:

Action: • It acts as an expectorant, increasing cough.

- It acts also as a mucolytic, decreasing viscosity of mucus.

Side effects:

- Disturbance of thyroid function.
- Irritation of eye (lacrimation and foreign body sensation), nose (sneezing and increased discharge), mouth (salivation and parotid swelling), and skin rash.

Dose: 300 mg/8 hours.

2- Ammonium chloride (*Bronchistal*, *Avipect* with pheniramine,) or carbonate.

3- Na⁺⁺ or K⁺ acetate or K⁺ citrate (*Coldal*, or *Osipect*):

4- Syrup Ipecac (*tincture ipecac*) (*Koffex* with ephedrine and ammonium chloride): It produces nausea.

5- Guaiphenesin (*Bronex*).

Antitussives

They are used for non-productive cough.

A) Peripheral anti-tussives:

They inhibit cough reflex by decreasing impulses from respiratory passages.

1- Demulcents e.g., liquorice lozenges; they are used for cough due to sore throat and laryngitis.

2- Drugs that depress pulmonary stretch receptors (and may have a local anesthetic action)

- Benzonotatate (*Tessalan* or *Bronchofree*).

- Carbetapentane (*Toclase*).

B) Central anti-tussives:

They inhibit cough center.

- Opioids as - Codeine (*Codipront*).
 - Dihydro-codeine (*Paracodin*).
 - Pholcodeine (*Marynol*).
- Non-opioids as - Noscapine (*Tusscapine*).
 - Dextro-methorphan (*Tussilar or Codilar*).
 - Levo-propoxyphene.
 - Antihistaminics as diphenhydramine or chlorpheniramine.
 - Butamirate (*Cough cut or Sinecod*).
 - Oxiladine (*Oxeladine, or Paxeladine*).

Surfactant Replacement Therapy

Physiological Considerations

Surfactant

Composition: It is a mixture of:

a) Lipids: (90%) which consist of:

- Dipalmitoyl phosphatidyl choline (DPPC) (70%). It decreases surface tension.
- Phosphatidyl glycerol (10%).
- Phosphatidyl ethanolamine.
- Sphingomyelin.
- Phosphatidyl inositol.
- Lysophosphatidyle choline.
- Neutral lipids.

b) Proteins (10%) (Surfactant associated proteins). There are 4 types:

- SP-A: a hydrophilic protein. It has the following functions:
 - It has a biological role in enhancing the effect of SP-B.
 - It regulates surfactant reuptake and secretion by type II cells.
 - It causes formation of tubular myelin (a form of alveolar surfactant).
 - It counteracts inhibition of surfactant by blood proteins.
 - It modulates host defense mechanisms.

- SP-B and SP-C: both are hydrophobic proteins.

They have an important role in generating the mono-molecular phospholipid layer.

- SP-D: It is involved in host defense (not involved in surface tension reduction).

Function of Surfactant:

1- It decreases surface tension:

- This is done by formation of a monomolecular phospholipids layer enriched in DPPC at the air-liquid interface.

SP-A causes formation of tubular myelin.

SP-B (enhanced by SP-A) and SP-C lead to generation of monomolecular phospholipids layer.

- Surfactant's ability to decrease surface tension is directly proportional to its concentration within the alveoli; as when the alveolus becomes smaller, surfactant becomes concentrated, so the surface tension decreases more and prevents the alveoli from collapse. When the alveolus becomes larger, surfactant becomes less concentrated, so the surface tension increases more and prevents the alveoli from expanding. Therefore, the net effect is stabilization of the size of alveoli.

2- It has an immunological function (involved in host defense) by SP-D.

Cellular Metabolism of Surfactant

Synthesis: in endoplasmic reticulum of type II pneumocytes.

Storage: in lamellar bodies.

Secretion: In the alveolar space as tubular myelin (lattice like structure) which is thought to be a precursor of monomolecular phospholipids.

Fate: • Reuptake: as monomolecular phospholipids will be changed to small vesicles which are taken-up by type II cells for degeneration or recycling.

- In injured lung, serum protein present in air space inactivates surfactant (figure 4-14).

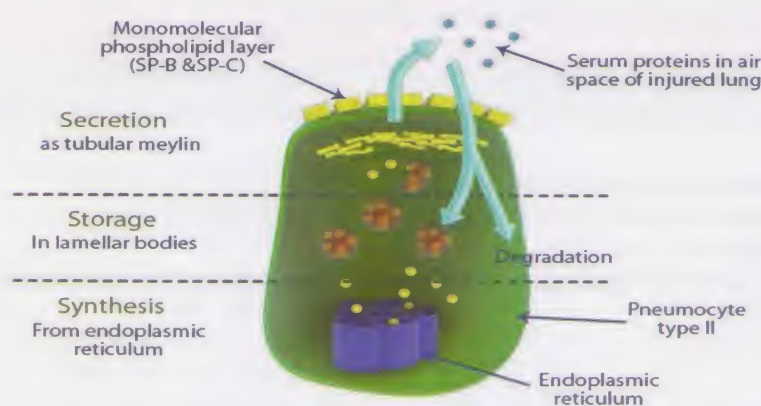


Figure 4-14: Cellular metabolism of surfactant

Source of Surfactant

It is obtained from the lung by whole lung lavage or broncho-alveolar lavage.

Then centrifugation is done yielding:

- Large surfactant aggregates (LSA): They are very surface active. They consist of lamellar bodies, tubular myelin and large vesicular structure.
- Small surfactant aggregates (SSA): They consist of a small vesicular structure.

Surfactant Alteration in ARDS

- 1- Surfactant production is decreased due to damage of alveolar epithelium type-II by proteases and toxic O_2 free radicals.
- 2- Alteration of surfactant metabolism with abnormal phospholipid synthesis occurs. This decreases phosphatidyl-choline and phosphatidyl glycerol, and increases sphingomyelin and lysophosphatidyle choline.
- 3- Inactivation by serum proteins occurs.
- 4- Decreased ability to form an effective phospholipid monolayer.
- 5- Increased small surfactant aggregates formation.

Value of Surfactant:

It increases compliance and gas exchange which decreases mortality.

Exogenous Surfactant Preparations:**1- Natural surfactant extracts:**

- They are produced from minced calf or porcine lungs by chloroform extraction of lung lavage material that has undergone differentiated centrifugation to isolate large surfactant aggregates fraction.
- They contain surfactant lipids, hydrophobic proteins SP-B and SP-C (but do not contain SP-A).

Advantage: excellent surface tension reducing ability.

Disadvantage: High cost and unavailability.

For example: Infasurf and Alveofact.

2- Modified (semi-synthetic) minced lung surfactant extracts:

- They are obtained from porcine or bovine sources as natural surfactant where after chloroform extraction, DPPC and palmitic acid are added to minced lung extract to increase biophysical activity.
- They contain small quantities of SP-B and SP-C.

Advantage: available (as they are obtained from animals other than the natural one).

Disadvantage: less effective as it contains low amount of SP-B and C.

For example: **Survanta**, surfactant TA, and Curosurf.

3- Synthetic surfactant:

It contains no proteins; therefore, it is less antigenic and does not transmit infections.

For example: 1- **ALEC** (Artificial Lung Expanding Compound) that is a lipid mixture of DPPC and PG.

2- **Exosurf**: It consists of DPPC and 2 spreading/adsorption agents (hexadecanol and tyloxapol). It may produce transient apnea in infants.

3- **ITL4**: Mixture of a lipid and a synthetic peptide based on the structure of SP-B.

4- Human surfactant:

- It is obtained by purification of surfactant isolated from amniotic fluid collected from caesarian sections for term pregnancy or from healthy subjects.

- It contains all surfactant lipids and proteins including SP-A.

Advantage: It is ideal for use.

Disadvantage: - High cost and unavailability.

- Risk of transmission of infection as cytomegalovirus, herpes, and HIV.

Uses:

In **respiratory distress syndrome in infants** (in ARDS, its role is not promising).

It is used in infants more than 700 gram weight. It produces the following actions:

- 66% reduction in mortality from RDS.
- Reduced incidence of bronchopulmonary dysplasia, pneumothorax, pulmonary interstitial edema, and patent ductus arteriosus.

Methods of Administration

a- Instillation:

A liquid bolus of exogenous surfactant is **instilled directly into the lung** via the endotracheal tube.

Advantages:

- A large dose can be given over a relatively short period of time (dose > 100 mg lipid/kg and volumes > 4 mL/kg).
- Rapid delivery and rapid response are obtained.

Disadvantages:

- A large bolus dose may obstruct the airway and create foaming when surfactant mixes with gases. This increases the PaCO₂ and peak airway pressure.
- It needs appropriate positioning to optimize distribution.
- High cost due to large dose.

b- Aerosolization:

Exogenous surfactant is given by aerosolization.

Advantages:

- Gentle delivery to the lung, so it does not obstruct the airway.
- Better distribution (especially if there is uniform lung injury).
- Cost effectiveness due to its small dose (3-5 mg/lipid/kg).
- Standardized technique.

Disadvantages:

- Mal-distribution if lung injury is heterogeneous, so less surfactant will be deposited in the areas of the lung that need it most.
- Slow delivery and slow response.

Dose:

a- Instillation: Large dose up to > 100 mg lipid/kg.

b- Aerosolization: small dose 3-5 mg lipid/kg.

Timing:

Early administration of exogenous surfactant is ideal.

DRUGS USED IN RENAL DISEASES

Vasoactive Drugs used in Renal Dysfunction

1- Sympathomimetics:

- Catecholamines: - Endogenous: • Adrenaline.
• Noradrenaline.
• Dopamine.
- Synthetic: • Dopexamine.
• Fenoldopam.
- Non-catecholamine: • Phenylephrine.
• Vasopressin and desmopressin.

2- Adenosine.

3- Calcium channel blockers.

4- ACE inhibitors.

These drugs were discussed before.

Diuretics

They are any substance that causes diuresis of water and sodium increasing urine output.

A) Diuretics Acting on the Nephrons:

- **Thiazides (Benzo-thiadiazide):** act at the **early part of distal** convoluted tubules and **proximal** convoluted tubules.
- **Loop (high ceiling) diuretics:** act at the **medullary thick ascending limb of the loop of Henle** and the **proximal** convoluted tubules.
- **Potassium-sparing diuretics:** act at the **late part of distal** convoluted tubules and **cortical collecting** ducts.
- **Osmotic diuretics:** act at the **proximal** convoluted tubules, **descending limb of loop of Henle**, and **collecting ducts**.
- **Carbonic anhydrase inhibitors (CAIs):** act at the **proximal** convoluted tubules (figure 4-15).

B) Other Drugs Used as Diuretics via Indirect Extrarenal Actions:

- 1) Drugs increase cardiac output which results in increased renal blood flow. This increases GFR which leads to diuresis: • Dopamine.
• Dobutamine.
• Digitalis.
• Aminophylline.
• Salt infusion.
- 2) Drugs mobilize edema fluid: i.v. albumin in hypoproteinemia.
- 3) Drugs inhibit antidiuretic hormone release:
 - Alcohol
 - Methylxanthines
 - Glucocorticoids
 - Water (a physiological diuretic)
- 4) Atrial natriuretic peptide (ANP):

It is a 28 amino acid peptide isolated from the atrial muscle cells. It stimulates specific receptors via guanylate cyclase increasing cGMP. This leads to:

- Increased Na^+ and H_2O renal excretion due to:
 - increasing glomerular filtration rate (GFR)
 - redistribution of the blood flow within the kidney (medullary washout)
 - decreasing renal reabsorption at the distal collecting ducts (direct action).
- Inhibiting aldosterone release.
- Smooth muscle relaxation.

ANP is released in response to increased cardiac filling pressure which increases atrial distension.

Uses: - Congestive heart failure.

- Hypertension.

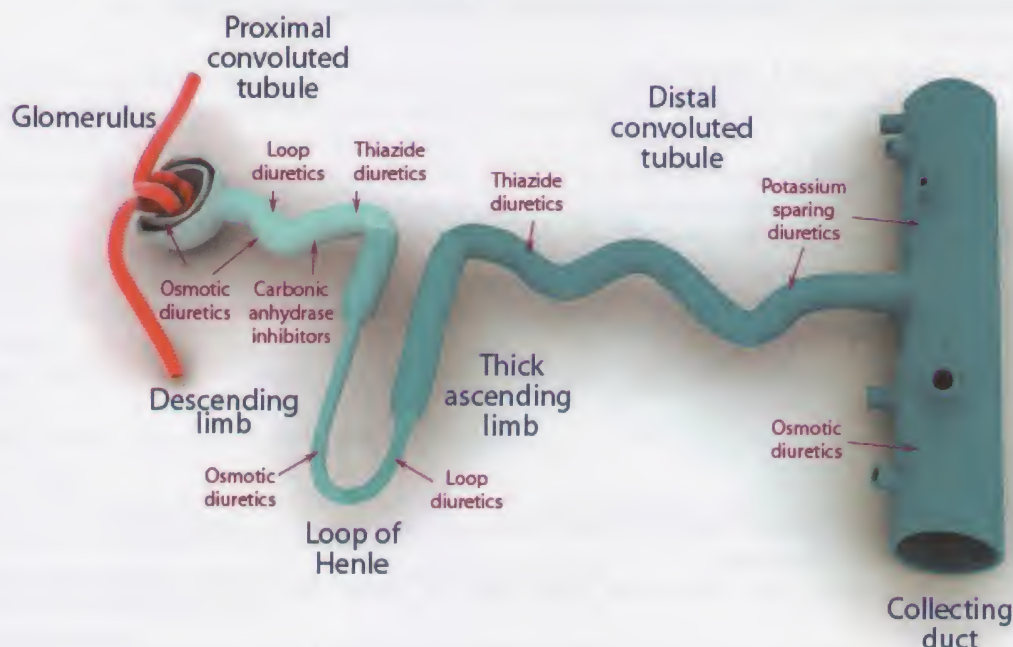


Figure 4-15: Sites of action of diuretics

	Thiazides (Benzo-thiadiazides)	Loop (High Ceiling) Diuretics
Potency	<ul style="list-style-type: none"> • Moderate efficacy diuretics. They excrete 5-10% of filtered Na^+. They are ineffective at low glomerular filtration rate (GFR) ($< 20 \text{ mL/min}$) except metolazone which is effective at this low GFR. 	<ul style="list-style-type: none"> • High efficacy diuretics. They excrete 15-25% of filtered Na^+. They are effective at low GFR even $< 10 \text{ mL/min}$.
Action	<p>1- Diuretic action: Site of action:</p> <ul style="list-style-type: none"> • The early distal tubules (diluting segment) (the main site). • The proximal convoluted tubules (the secondary site of action). <p>Mechanism of action: They increase Na^+, Cl^-, K^+, and H^+ excretion by:</p> <ul style="list-style-type: none"> • inhibition of reabsorption of Na^+ and Cl^- co-transport in the above sites. <p>Some agents inhibit carbonic anhydrase enzyme resulting in increased HCO_3^- secretion which causes alkalinization of the urine.</p> <p>2- Increased Ca^{++} reabsorption in the early part of distal convoluted tubules resulting in decreased Ca^{++} excretion.</p> <p>There is also increased Mg^{++} excretion.</p> <p>3- Decreased uric acid excretion leading to an increase in its plasma level.</p> <p>4- Paradoxical anti-diuretic action in nephrogenic diabetes insipidus (antidiuretic hormone resistant type) resulting in decreased polyurea and polydipsia.</p> <p>Increased Na^+ excretion causes electrolyte depletion and decreased extracellular volume and GFR. This allows a large fraction of</p>	<p>1- Diuretic action: Site of action:</p> <ul style="list-style-type: none"> • The luminal surface of the medullary thick ascending limb (mTAL) of the loop of Henle (the main site of action). • The proximal convoluted tubules (the secondary action). <p>Mechanism of action: They increase Na^+, Cl^-, K^+, and H^+ excretion by:</p> <ul style="list-style-type: none"> • inhibition of reabsorption of Na^+ and Cl^- co-transport in the above sites. <p>They have high ceiling effect (i.e., increasing doses lead to increasing diuresis).</p> <p>N.B.: Renal hypoperfusion increases Na-Cl reabsorption in mTAL. This increases O_2 consumption in the front of decreased O_2 delivery. When ATP stores become depleted, active Na-Cl reabsorption winds down. This increases Cl^- concentration in tubular fluid that on reaching the macula densa, angiotensin release occurs. This causes afferent arteriolar vasoconstriction (i.e., tubulo-glomerular feedback) with a decrease in GFR which leads to decreasing solute reabsorption and decreasing mTAL O_2 consumption. So, O_2 balance occurs. Therefore, theoretically, loop diuretics or dopaminergic agents decrease the ischemic and nephro-toxic insult to the tubules by inhibiting Na-Cl reabsorption in mTAL which decreases O_2 consumption. This enhances O_2 balance i.e., renal protection (see later).</p>

	<p>glomerular filtrate to be reabsorbed by the proximal convoluted tubules and decreases delivery of Na^+ and water to the distal convoluted tubules.</p> <p>5- Antihypertensive action: by;</p> <ul style="list-style-type: none"> • Natriuresis (increased Na^+ excretion) • Direct arteriolo-dilatation. • Decreasing vascular receptor sensitivity to vasopressor agents. • Affection of prostaglandin synthesis; a vasodilator prostaglandin may be involved. 	<p>2- Increased Ca^{++} and Mg^{++} excretion.</p> <p>3- Decreased uric acid excretion.</p> <p>4- Vasodilatation that results in:</p> <ul style="list-style-type: none"> • Increasing renal blood flow. • Blood distribution from renal medulla to the cortex. • Decreasing left ventricular filling pressure and decreasing pulmonary congestion. <p>5- Furosemide decreases intracranial pressure as it mobilizes edema fluid and decreases cerebrospinal fluid production (in contrast to mannitol, a disrupted blood-brain barrier does not influence the effect of furosemide on intracranial pressure).</p> <p>6- Furosemide enhances the effect of non-depolarizing muscle relaxants.</p>
Onset and Duration	<ul style="list-style-type: none"> • Onset: oral: 1 hour. • Duration: oral: 10-72 hours. 	<ul style="list-style-type: none"> • Onset: - Oral: 1 hour - I.v. 2-10 min. • Duration: - Oral: 4-6 hours. - I.v. 2 hours. <p>30% is metabolized and excreted in gastrointestinal tract and 70% is excreted via the kidneys.</p>
Uses	<ol style="list-style-type: none"> 1- Edema due to - mild or moderate heart failure - renal disease. 2- Idiopathic hypercalciuria in patients with recurrent renal stones. 3- Nephrogenic diabetes insipidus. 4- Hypertension (initial therapy or in combination with other agents). 	<ol style="list-style-type: none"> 1- Edema: <ul style="list-style-type: none"> - Acute pulmonary edema (due to its diuretic and pulmonary vasodilating effect). - Refractory edema. 2- Hypercalcemia. 3- Hypertensive encephalopathy and cerebral edema. 4- Conversion of oliguric renal failure to non-oliguric renal failure (in the early stage). 5- Evaluation of acute oliguria where 10-20 mg furosemide is given: <ul style="list-style-type: none"> • If hypovolemia, little or no response occurs. • If oliguria due to redistribution of renal blood flow to juxta-medullary nephrons, resumption of normal urine output occurs. 7- Forced diuresis for poisoning such as barbiturate poisoning.
Side effects (they are detected from the action)	<ol style="list-style-type: none"> 1- Hypovolemia. 2- Hypokalemia; therefore, it is avoided in: <ul style="list-style-type: none"> • Liver cirrhosis as it causes hepatic coma. • Digitalis arrhythmias because thiazides increase toxicity. 3- Hypochloremic metabolic alkalosis (loss of chloride and hydrogen ions). 4- Hyperuricemia, so it is avoided in gout diseases. 5- Hyperglycemia, so it is avoided in diabetes mellitus and with steroid therapy as it inhibits insulin release and blocks peripheral glucose utilization. 6- Gastrointestinal side effects: nausea, epigastric discomfort, and abdominal cramps. 7- Hypercalcemia. Hypomagnesemia. 8- Hypercholesterolemia, hyperlipidemia, and decreased high density lipoproteins (HDL) i.e., it is atherogenic. 9- Allergy as skin rash, thrombocytopenia and acute pancreatitis. 10- Weakness, fatigability, ad impotence. 	<ol style="list-style-type: none"> 1, 2, 3, 4, 5, and 6 as thiazides, in addition to: 7- Hypocalcemia, hypercalciuria and renal stones. 8- Reversible ototoxicity: especially with ethacrynic acid, rapid injection, and if associated with aminoglycosides. 9- Allergic reactions as acute allergic interstitial nephritis. 10- Muscle pain especially with bumetanide.
Doses and preparations	<p>They are given as:</p> <ul style="list-style-type: none"> - a single morning dose. - an intermittent therapy (5 days on and 2 days off). <p>1- Thiazides:</p> <ul style="list-style-type: none"> • Chlorothiazide (<i>Diuril</i>) 	<p>1- Furosemide (<i>Lasix, Salex, Odement, or Lafurex</i>):</p> <ul style="list-style-type: none"> - Oral: 20-120 mg/day (0.75-3 mg/kg) (20-40 mg tablets). - I.v. or i.m.: 20-120 mg (0.1-1 mg/kg) (20-40 mg ampoule). <p>2- Ethacrynic acid (<i>Edecrin</i>)</p>

<ul style="list-style-type: none"> • Hydrochlorothiazide (<i>Hydrex, Hydrodiuril, Microzide</i>) 25-100 mg/day. • Hydroflumethiazide 25-100 mg/day. • Bendroflumethiazide 2.5-10 mg/day. • Cyclothiazide 1-2 mg/day. <p>2- Diuretics related to thiazides: Long duration (42-72 hours).</p> <ul style="list-style-type: none"> • Chlorthalidone (<i>Hygroton or Thalitone</i>). • Metolazone (<i>Metenix, Zaroxolyn, or Mykrox</i>) (it can act with low GFR). • Clopamide • Mefruside. <p>3- Indapamide (<i>Natrilix, Lozol or Diurex</i>):</p> <ul style="list-style-type: none"> - It is the only thiazide diuretic with biliary excretion; therefore, it can be used in patients with renal insufficiency. - It acts by decreasing Ca^{++} influx in the smooth muscles of the blood vessels resulting in vasodilatation; therefore, it is used as antihypertensive (it is not used to treat edema). - It has little effects on K^+, glucose, or uric acid excretion. 	<ul style="list-style-type: none"> - Oral: 50-200 mg/day. - I.v.: 50 mg. <p>It is not taken by i.m. or subcutaneous route as it is a very irritant drug.</p> <p>3- Bumetanide (<i>Burinex, Bumex or Edemex</i>): 0.5-4 mg i.v. over 1-2 min (more potent than furosemide).</p> <p>4- Torsemide (<i>Demadex</i>): 10-100 mg.</p> <p>5- Piretanide: 6 mg. It causes vasodilatation, so it is used as an antihypertensive agent.</p> <p>Drug interaction:</p> <ol style="list-style-type: none"> 1- Ethacrynic acid and furosemide displace warfarin and clofibrate from plasma proteins. 2- With lithium, excretion is decreased. 3- With cephalosporins or aminoglycosides: the risk of nephrotoxicity and ototoxicity is increased. 4- With non-steroidal anti-inflammatory drugs; the natriuretic and hypotensive effect of furosemide is decreased. 5- Ethacrynic acid aggravates corticosteroid-induced gastric hemorrhage.
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	K ⁺ -Sparing Diuretics		Osmotic Diuretics	Carbonic Anhydrase Inhibitors (CAIs)
Potency	<ul style="list-style-type: none"> • Low efficacy diuretics. They excrete 5% of filtered Na^+. 		<ul style="list-style-type: none"> • Moderate efficacy diuretics. They excrete 5-10% of filtered Na^+. 	<ul style="list-style-type: none"> • Low efficacy diuretics.
Action	<p>a) Competitive (aldosterone antagonists)</p> <p>1- Diuretic action:</p> <p><u>Site of action:</u></p> <ul style="list-style-type: none"> • Late part of distal convoluted tubules and cortical collecting ducts. <p><u>Mechanism of action:</u></p> <ul style="list-style-type: none"> • It increases Na^+ and Cl^- excretion. • It decreases K^+ and H^+ excretion. It competes with aldosterone for its cytoplasmic receptor sites in the distal convoluted tubules as it prevents translocation of the receptor complex to the nucleus. This effect is increased in hyper-aldosteronism. 2- They increase Ca^{++} excretion. 	<p>b) Non-competitive (non-aldosterone antagonists)</p> <p>1- Diuretic action:</p> <p><u>Site of action:</u></p> <p>The same as aldosterone antagonists.</p> <p><u>Mechanism of action:</u></p> <ul style="list-style-type: none"> • They increase Na^+ excretion and decrease K^+ excretion by direct action as they block Na^+ channels at the luminal border. • Amiloride causes: <ul style="list-style-type: none"> - inhibition of Na^+-K^+ ATPase acting on collecting ducts. - inhibition of Na^+-H^+ exchange mechanisms in proximal tubules. This effect is increased in absence of hyper-aldosteronism. 2- Amiloride causes: <ul style="list-style-type: none"> • Decreased Ca^{++} excretion. • Positive inotropic 	<p>1- Diuretic action:</p> <p><u>Site of action:</u></p> <p>Proximal convoluted tubules.</p> <p><u>Mechanism of action:</u></p> <ul style="list-style-type: none"> • They are non-competitive inhibitors of carbonic anhydrase enzyme. <p>$\text{H}_2\text{O} + \text{CO}_2 \xrightarrow{\text{carbonic anhydrase}} \text{H}_2\text{CO}_3 \rightarrow \text{HCO}_3^- + \text{H}^+$</p> <p>$\text{H}^+$ is exchanged with Na^+ leading to Na^+ reabsorption. Therefore, CAIs block carbonic anhydrase action, leading to decreased tubular H^+ excretion, therefore, Na^+, K^+, HCO_3^-, and H_2O excretion are increased, resulting in alkaline urine with retention of Cl^- instead of HCO_3^- to maintain an ionic balance. • They inhibit phosphate and Ca^{++} reabsorption leading to increased phosphate and Ca^{++} excretion. • They are weak diuretics because their effects are limited by the reabsorption capacities of the more distal segment of nephrons. <p>2- Ocular action:</p> <p>CAIs decrease the rate of aqueous humor formation decreasing intraocular pressure.</p> <p>3- Central nervous action:</p> <ul style="list-style-type: none"> • CAIs decrease epileptic fits. • CAIs decrease the rate of </p>	<p>1- Diuretic action:</p> <p><u>Site of action:</u></p> <p>1- Proximal convoluted tubules.</p> <p>2- The descending limb of loop of Henle.</p> <p>3- The collecting duct.</p> <p><u>Mechanism of action:</u></p> <ul style="list-style-type: none"> • They are osmotically active diuretics which are filtered freely via the glomeruli (they have limited reabsorption). This increases the osmotic pressure in the proximal tubules resulting in decreased passive water reabsorption which in turn increases water excretion. • On large doses, they increase Na^+, Cl^-, and K^+ excretion. <p>2- Mannitol causes:</p> <ul style="list-style-type: none"> • Prostaglandin-mediated increased renal medullary blood flow which leads to partial washout of normal medullary hypertonicity. This interferes with renal concentrating ability.

	<p>3- They may decrease uric acid excretion.</p> <p>4- They have some anti-androgenic actions.</p>	<p>action.</p> <ul style="list-style-type: none"> • Anti-arrhythmic action as it prolongs the absolute refractory period without affecting the V_{max}. 	<ul style="list-style-type: none"> • O_2 free radical scavenging which decreases tubular endothelial cell swelling 	<p>cerebrospinal fluid formation due to metabolic acidosis or increased local CO_2 tension.</p> <ul style="list-style-type: none"> • CAIs stimulate respiration.
Onset and duration	<ul style="list-style-type: none"> • Onset: 2 hours • Duration: 24 hours • It is metabolized by the liver to active metabolites (canrenone) which is given parenterally. 	<ul style="list-style-type: none"> • Onset: 2 hours. • Duration: <ul style="list-style-type: none"> - Amiloride: 12-16 hours. - Triamterene: 10 hours. • Amiloride 50% excreted unchanged in the urine. • Triamterene is metabolized by the liver to active metabolites (hydroxy-triamterene). 	<ul style="list-style-type: none"> • Mannitol: <ul style="list-style-type: none"> Onset: 30-60 min Duration: 6-8 hours. It is not metabolized, but excreted unchanged via the kidneys. • Urea: <ul style="list-style-type: none"> Onset: 30-45 min Duration: 5-6 hours • Glycerine: <ul style="list-style-type: none"> Onset: 10-30 min Duration: 4-5 hours. • Isosorbide: <ul style="list-style-type: none"> Onset: 10-30 min Duration: 5-6 hours. 	<ul style="list-style-type: none"> • Onset: 2 hours. • Duration: 12 hours. • Acetazolamide is not metabolized, but excreted almost unchanged by the kidney within 24 hours.
Uses	<ol style="list-style-type: none"> 1- Refractory edema (with other diuretics). 2- Hyperaldosteronism (primary and secondary) e.g., liver cirrhosis, heart failure, Conn's syndrome 3- Hypokalemia or with drugs that cause hypokalemia e.g., thiazides. 	<ol style="list-style-type: none"> 1- Edema as congestive heart failure. 2- Secondary hyperaldosteronism by Triamterene. 3- Mild hypertension (with others as thiazides) by amiloride. 4- Ventricular tachycardia by amiloride. 	<ol style="list-style-type: none"> 1- To maintain high urine output to prevent acute renal failure e.g., massive hemolytic reactions, massive trauma, surgery, jaundice or rhabdomyolysis. 2- Forced diuresis in barbiturate or salicylate toxicity. 3- As a dehydrating measure to decrease intraocular and intracerebral pressures. 4- Evaluation of acute oliguria as small dose 0.2 gm/kg is given: <ul style="list-style-type: none"> • If there is hypovolemia, the urine output is increased. • If there is severe glomerular or tubular injury, little effect occurs. 	<ol style="list-style-type: none"> 1- Glaucoma (the main usage). 2- To alkalinize the urine, in treating acidic drugs toxicity as barbiturate toxicity. 3- Metabolic alkalosis if other measures fails. 4- As an adjuvant drug in epilepsy. 5- Prophylaxis against acute mountain sickness due to respiratory stimulation. 6- Familial periodic paralysis as it induces acidosis, increasing extracellular K^+ locally in the muscles. 7- Hyperphosphatemia. 8- Increased intracranial tension.
Side effects	<ol style="list-style-type: none"> 1- Hyperkalemia especially in patients: <ul style="list-style-type: none"> • on high K^+ intake • with renal dysfunction • with β blockers • on ACE inhibitors. 2- Metabolic acidosis especially in decompensated hepatic failure. 3- Hyperuricemia. 4- Allergy. 5- Gastrointestinal effects as nausea, abdominal pain, and diarrhea. 6- Endocrine effects: <ul style="list-style-type: none"> • In males, gynecomastia and impotence. • In females, menstrual 	<ol style="list-style-type: none"> 6- Amiloride: causes paresthesia, depression, muscle weakness, and cramps. 7- Triamterene causes renal stones 	<ol style="list-style-type: none"> 1- Acute increase in intravascular volume, resulting in: <ul style="list-style-type: none"> • Precipitation of heart failure and pulmonary edema especially in patients with limited cardiac reserve or with severe renal failure. • Dilutional transient Hyponatremia. • Hemodilution (decreased Hb concentration). 2- Increased intracerebral hemorrhage especially in newly born. 3- Hypovolemia, hypokalemia, and 	<ol style="list-style-type: none"> 1- Mild hyper-chloremic metabolic acidosis due to its limited effects on the distal tubules. 2- Phosphaturia and hypercalciuria, resulting in increased Ca^{++} phosphate stones. 3- Alkalinization of the urine which decreases excretion of alkaline drugs as quinidine. 4- On large doses; drowsiness, paresthesia, and confusion. 5- Allergy as fever, rash, and bone marrow depression. 6- It precipitates hepatic encephalopathy in liver cirrhosis due to passage of ammonia into the systemic circulation.

	disturbances and hirsutism.	and renal toxicity especially with non-steroidal anti-inflammatory drugs.	<p>Hypernatremia (due to loss of water > loss of Na⁺).</p> <p>4- In head trauma, if the blood brain barrier is not intact, mannitol may enter the brain and with draw water and cause rebound cerebral swelling.</p> <p>5- Mannitol may cause allergic reactions.</p> <p>6- If urea is extravasated, thrombosis and pain may occur.</p> <p>7- Glycerol may cause hyperglycemia and glucosuria.</p>	
Doses and preparations	<ul style="list-style-type: none"> • Spironolactone (<i>Aldactone</i>) (<i>Aldactazide</i> with hydro-chlorothiazide) (<i>Lasilactone</i> with furosemide) Oral: 25mg/6 hours. • Potassium canrenoate: i.v.: 200-400 mg 	<p>1- Amelorida (<i>Midamor</i> or <i>Moduretic</i> with hydro-chlorothiazide): Oral: 5-20 mg</p> <p>2- Triamterene (<i>Dyrenium</i> or <i>Epitens</i> with xipamide): Oral: 200-300 mg</p>	<ul style="list-style-type: none"> • Mannitol (10-25%): i.v.: 0.25-1.0 gm/kg. • Urea 30%: i.v.: 1.5 gm/kg/day. <p>Isosmotic solution of dextrose is added to avoid hemolysis induced by pure urea solution.</p> <ul style="list-style-type: none"> • Glycerol (glycerine): Oral: 1.5 gm/kg/day. • Isosorbide: Oral 1.5 gm/kg/day. 	<p>1- Acetazolamide (<i>Diamox</i>): 250-500 mg oral, i.v., or i.m.</p> <p>2- Dichlor-phenamide: 50 mg/8 hours orally.</p> <p>3- Ethoxazolamide: 125 mg/ 8 hours orally.</p> <p>4- Methazolamide: 50 mg/8 hours orally.</p>

Diuretics and Renal Protection

Diuretics (furosemide and mannitol) are often used to protect the kidneys during ischemic episodes such as aortic cross-clamping and cardiopulmonary bypass, but **human studies have failed to show the effectiveness of these agents in the prevention of ischemic acute renal failure**. There is also no clear evidence that polyuric renal dysfunction has a better outcome than oliguric renal failure. It is generally accepted that the intensive care management of critically ill patients is easier if there is a urine output.

GASTROINTESTINAL DRUGS

Histamine Antagonists

Histamine Physiology

Synthesis:

Synthesis and catabolism of histamine are discussed in figure 4-16.

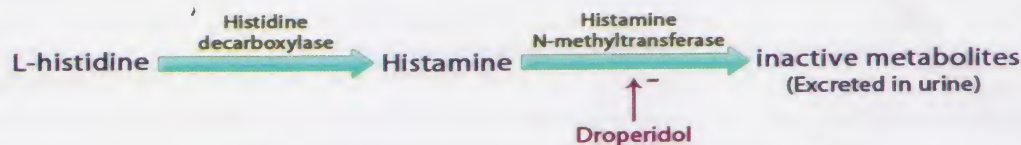


Figure 4-16: Synthesis and catabolism of histamine

Histamine is stored in mast cells and basophils especially in tissues exposed to external environment e.g., skin, lungs, and gastrointestinal tract.

Causes of Histamine Release:

1- Drug-Induced (Non-Immunological Release) (Anaphylactoid Reaction):

It is due to the direct action of drugs on cells (mainly mast cells) leading to release of their chemical mediators. It has no immunological basis and does not depend on IgE production.

The clinical pictures are like anaphylaxis, but usually benign, as vasodilatation, urticaria along the vein e.g., morphine, thiopentone, atracurium, dextran, or atropine.

2- Immunological Reaction:

For example, type I hypersensitivity reactions.

3- Chemical and Mechanical Mast Cell Injury.

Mechanism of Action

There are 3 receptor types:

- H₁ receptor: acts via G_q.
- H₂ receptor: acts via G_s.
- H₃ receptor: acts via G_i. It is primarily located on histamine-secreting cells and mediates negative feedback, inhibiting the synthesis and release of additional histamine.

Action:

	H ₁ receptor (Clinical Picture of Anaphylactic Shock)	H ₂ receptor
1- Respiratory actions	• Bronchoconstriction.	• Mild bronchodilatation.
2- Cardio-vascular actions	<ul style="list-style-type: none"> • Peripheral, coronary, and central venous vasodilatation resulting in a decrease in the venous return and drop of blood pressure with reflex tachycardia. • Pulmonary vasodilatation. • Ventricular irritability. 	<ul style="list-style-type: none"> • Pulmonary vasoconstriction. • Positive chronotropic and inotropic actions due to: <ul style="list-style-type: none"> - Direct action on cardiac H₂ receptors. - Catecholamine release from adrenal medulla. - Stimulation of baroreceptor reflex.
3- Central nervous actions	• Cerebral vasodilatation resulting in transient increase in cerebrospinal fluid pressure which leads to headache (histamine cephalgia).	
4- Dermal actions	<ul style="list-style-type: none"> • Triple response (classical wheel and flare response) which causes: <ul style="list-style-type: none"> - Outer flush due to arteriolar dilatation. - Inner red spot due to capillary dilatation. - Central wheel due to increased capillary permeability (edema). 	
5- Gastro-intestinal actions	• Contraction of intestinal smooth muscles leading to diarrhea.	• Stimulation of parietal cells resulting in increased gastric acid secretion.
6- Uterine actions	• Contraction.	
7- Immuno-logical actions	• Attraction of leukocytes and induction of prostaglandins synthesis	• Activation of suppressor T lymphocytes.

To Antagonize the Actions of Histamine

- 1- Physiological antagonism: epinephrine is useful in anaphylaxis.
- 2- Competitive antagonists: antihistaminics (H_1 and H_2 blockers).
- 3- Prevention of histamine release: by mast cell stabilizers e.g., corticosteroids, cromoglycate, ketotifen, and that drugs increase cAMP as β_2 agonists and aminophylline.
- 4- Desensitization: by gradually increasing the doses of the antigen.

H₁-Receptor Antagonists

Mechanism of Action:

They produce reversible competitive blockade of H_1 receptors.

Preparations and Doses:

A) First Old Generation:

- 1- Ethanolamines:
 - Dimenhydrinate (*Dramamine, Dramenex, or Sultan*) 50 mg.
 - Diphenhydramine (*Benadryl*) 25 mg.
 - Clemastine (*Tavegil*) 1 mg.
 - Dimethindine (*Fenistil*)
- 2- Ethylene-diamines:
 - Antazoline 100 mg.
 - Mepyramine 100 mg.
- 3- Alkylamines:
 - Pheniramine (*Avil*) 50 mg.
 - Chlorphenoxamine (*Allergex*) 20 mg.
 - Chlorpheniramine (*Anallerg*) 4 mg.
 - Dexchlorpheniramine (*Polaramine*) 4 mg.
- 4- Phenothiazines:
 - Promethazine (*Phenergan*) 25 mg. It may produce apnea in children.
 - Trimperazine 2.5 mg.
 - Cyproheptadine (*Triactin or Periactin*).
 - Mequitazine (*Primalan*)
- 5- Piperazines:
 - Cyclizine
 - Meclizine (*Antivert*) 25 mg.
 - Hydroxyzine (*Atarax or Vistaril*) 10 mg

B) Second New Generation:

They have no sedative (they do not cross blood brain barrier) or anticholinergic actions and they have long $t_{1/2}$ 12-24 hours:

- Terfenadine (*Triludan, Fastel, or Histamol*) 60 mg.
- Fexofenadine (*Allertam, Allerfen, Fastfen, Fexodine, Rapido, or Telfast*): an active metabolite of terfenadine.
- Astemizole (*Hismanal*) 10 mg
- Loratadine (*Claritine*).
- Acrivastine (*Semprex*).
- Cetirizine (*Alerid, Cetritin, Cetrak, Histazine-1, Tomazine, and Zyrtec*).
- Ebastine (*Astin, Ebastel, or Evastine*).
- Loratadine (*Claritine, Lorano, Loratan, or Mosedin*)
- Azelastine.

Actions:

1- Antihistaminic Action (H_1 -Receptor Blockade):

They oppose all H_1 effects due to the liberated histamine.

2- Anticholinergic Action (Atropine-Like Action): by the first generation.

For example, dryness of secretion.....etc.

3- Central Nervous Action:

- **Sedation and hypnosis:** by the first generation

In children, they may cause central nervous excitation resulting in agitation and convulsions.

- **Antiemetic action:** they inhibit vomiting center and prevent stimulation of vomiting center by impulses from vestibular nuclei.

- **Antiparkinsonian action:** due to their anticholinergic action.

4- Other Actions:

- Local anesthetic action.
- Anti-serotonin action e.g., cyproheptadine.
- Weak α blocking and anti-dopaminergic actions e.g., phenothiazines.

Pharmacokinetics:

- They have rapid oral absorption.
- They are widely distributed all over the body including central nervous system.
- They are metabolized mainly in the **liver**.

Indications:**M Due to their Antihistaminic Action:**

- Allergic reactions e.g., urticaria, rhinitis, and hay fever.
- Acute anaphylactic reactions: they have **limited value** (epinephrine is the drug of choice) because:
 - Although H₁ blockers prevent bronchoconstriction of histamine, they are ineffective in treating bronchial asthma or relieving bronchospasm associated with anaphylactic reaction because there are other mediators.
 - H₁ blockers are less effective in preventing hypotensive effect of histamine unless H₂ blockers are given concomitantly.
- Protection against drug-induced allergic reactions (e.g., intravenous radiocontrast, chymopapain injection for lumbar disc diseases, protamine) if used with H₂-receptor antagonists.

N Due to their Antiemetic Action:

- Motion sickness, Ménière's disease, and vestibular disturbance especially by diphenhydramine and promethazine.
- Suppression of cough and dyskinesia (e.g., Parkinsonism, drug-induced extrapyramidal side effects)
- Nausea and vomiting of pregnancy especially by doxylamine.
- As a premedication due to antiemetic and sedative hypnotic actions especially diphenhydramine, promethazine, and hydroxyzine.

O Due to the Anti-Serotonergic Action:

- Cyproheptadine is used in the management of Cushing's syndrome, carcinoid syndrome and vascular (cluster) headache.

Side Effects:

- 1- Due to atropine-like action: side effects as that of atropine action such as tachycardia...etc.
- 2- Due to central nervous action: sedation and drowsiness. Agitation and convulsions may occur in children.
- 3- Drug allergy especially with the topical use.
- 4- Teratogenicity especially with piperazine derivatives.

Drug Interactions:

- The first generation, with their sedative effect, potentiates other central nervous depressant drugs as barbiturates, benzodiazepines, and opioids.

H₂-Receptor Antagonists

Mechanism of Action: They produce reversible competitive blockade of H₂ receptors.

Preparations and Doses:

Drug	Onset	Duration	Potency	Dosage
Cimetidine (Tagamet)	1-2 hours	4-8 hours		<ul style="list-style-type: none"> • Oral: 400 mg/12 hours for at least 4 weeks then 400 mg once for the next 6 months to treat peptic ulcer. • I.v. or i.m. 300 mg 2 hours before anesthesia as a premedication.
Ranitidine (Zantac)	1-2 hours	8-10 hours	10 times more potent than cimetidine.	<ul style="list-style-type: none"> • Oral: 150 mg/12 hours. • I.v. or i.m. 50 mg 2 hours before anesthesia as a premedication.
Famotidine (Pepcid, Antodine, Famotak, or Pepotec)	1-3 hours	10-12 hours	10 times more potent than ranitidine	<ul style="list-style-type: none"> • Oral: 20 mg/12 hours • I.v. 20 mg 2 hours before anesthesia as a premedication.
Nizatidine (Axid, or Axid-free)	It is similar to ranitidine in action, doses and potency.			<ul style="list-style-type: none"> • I.v.: 100 mg 2 hours before anesthesia as a premedication.

Actions:

They **decrease gastric HCl secretion** especially during fasting and nocturnal acid secretions with less effect in meal stimulated and daytime acid secretion.

Gastric HCl secretion is stimulated by histamine, gastrin, cholinergic drugs and vagal stimulation. They have no effects on the lower esophageal sphincter pressures and the rate of gastric emptying.

Pharmacokinetics:

- They have rapid oral absorption. Their peak effect occurs after 2 hours.
- They are **excreted mainly by kidneys**; therefore, their doses are decreased in renal dysfunction.

Indications:

- 1- Duodenal and gastric ulcers.
- 2- Stress ulcers in critically ill patients.
- 3- Hyper-secretory states as Zollinger- Ellison's syndrome and multiple endocrine neoplasia.
- 4- **As a premedication** drug to decrease the risk of aspiration. They affect gastric pH for only those gastric secretions occurring after their administration.
- 5- Gastroesophageal reflux disease (GERD).
- 6- Bleeding esophageal varices.
- 7- Ranitidine (with bismuth, tetracycline, clarithromycin, and metronidazole) treats peptic ulcer associated with *Helicobacter pylori* infection.

Side Effects:

- 1- **Tolerance and rebound hyperacidity** with recurrence on withdrawal due to up-regulation of H_2 receptors.
- 2- **Hypochlorohydria**: i.e., decreased HCl in the gastrointestinal tract causes colonization of the stomach by bacteria which reduce salivary and dietary nitrates to nitrites. The latter are **carcinogenic nitroso compounds**.
- 3- **Rapid i.v. injection may cause bradycardia, hypotension, and even cardiac arrest** (this is mainly with cimetidine, less with ranitidine, and absent with famotidine).
- 4- **Diarrhea, nausea, and vomiting** may occur.
- 5- **Arthralgia, myalgia, and fatigue** may occur.
- 6- **Hypercholesterolemia, galactorrhea, and gynecomastia**.
- 7- Side effects of specific agents:
 - **Chronic** administration of **cimetidine** causes **hepatotoxicity, interstitial nephritis, headache, dizziness, confusion up to convulsions and disturbed level of consciousness especially in elderly and critically ill patients**. **Antiandrogenic action** may occur such as loss of libido, impotence, decreased sperm count due to blockage of androgen receptors. It may cause **bone marrow depression** resulting in granulocytopenia and thrombocytopenia.
 - **Ranitidine** has very few side effects as compared to cimetidine.
 - **Famotidine** causes **bronchial asthma and headache**. It produces very few side effects because it does not cross the blood brain barrier and thus has no neurological side effects. It does not block androgen receptors as well, thus has no anti-androgenic action.
 - **Nizatidine** has **cholinergic action** (as lacrimation, salivation, miosis, and diarrhea), mild **anemia**, and mild **elevation of serum cholesterol and uric acid**.

Drug Interactions:

- Cimetidine: decreases hepatic blood flow and inhibits cytochrome P-450 enzyme system resulting in decreased metabolism of many drugs; therefore, the doses of these drugs should be decreased about 50% with cimetidine such as lidocaine, phenytoin, diazepam, morphine, propranolol, theophylline, phenobarbitone, and warfarin.

Other agents have a very few drug interactions.

Proton Pump Inhibitors

Agents

- Omeprazole (*Losec, Fastcure, Gasec, Gastrocure, Gastrazole, Hyposecor, Napizole, or Omepack*).
- Lansoprazole (*Prevacid, Lantanon, Lanzor, Lopral, Loral, Peptazol, or Zoton*).
- Pantoprazole (*Prontonix, Controloc, Delpanto, Pantazole, Perloc, or Protofix*).
- Rabeprazole (*Aciphex, Bepra, Idizole, or Pariet*).
- Aripiprazole (*Aripiprex*).
- Esomeprazole (*Nexium*).

Mechanism of Action:**A) HCl Acid Suppression:**

- They are the **most potent** and the most efficient acid suppressant agents. They are arranged as regard potency from the higher to the lower as pantoprazole, lansoprazole, and omeprazole.
- They are protonated and trapped in the secretory canaliculi of the parietal cells, **inhibiting H^+/K^+ ATPase enzyme**. This leads to **inhibition of H^+ pump** that in turn **decreases HCl secretion** and elevates intragastric pH more than 4 for at least 20 hours in the nocturnal and day-times.
- This inhibition is **irreversible by omeprazole** and **reversible by other proton pump inhibitors**.

B) Anti-Helicobacter Pylori Action:

- They have a **direct bactericidal action**.
- **Decreasing gastric juice volume increases the concentration of antibiotics**.
- An increase in intragastric pH leads to a decrease in degradation of both acid-labile antibiotics and helicobacter pylori-specific immunoglobulins.
- **Lansoprazole** has an **anti-inflammatory action** decreasing host-bacteria interactions. It is the **most potent against the helicobacter pylori**.

Indications:**1- Duodenal and gastric ulcers:**

- They are used in severe refractory cases where they relieve the pain and promote healing.
- Pantoprazole is the most potent and efficient.

2- Gastroesophageal reflux disease (GRED):

- Lansoprazole is the most efficient in mild cases due to its rapid rate of absorption.
- Omeprazole is the most efficient in severe cases as it produces dose-dependant acid suppression.

3- Zollinger-Ellison syndrome.

Their use in aspiration prophylaxis prior to general anesthesia is limited.

4- Immuno-Modulators:

They inhibit several leukocyte functions; reduce chemotaxis and superoxide anion generation.

Pharmacokinetics:

- They are well absorbed orally especially pantoprazole.
- Onset: 1 hour.
- Peak: 2 hours.
- The bioavailability of lansoprazole and omeprazole decreases markedly (50%) if they are taken with food, they must be taken at least 30 minutes before meals, while pantoprazole is unaffected by food.
- They are mainly metabolized by the liver.
- Their plasma $t_{1/2}$ is 1 hour, but their duration of action is more than 24 hours due to prolonged inhibition of H^+/K^+ ATPase enzyme.

Side Effects: They are dose-dependent.

- **Recurrence:** less than H_2 antagonists.
- **Hypochlorohydia:** more than H_2 antagonists.
- **Neurological effects:** headache, dizziness, and somnolence.
- **Gastrointestinal effects:** diarrhea, constipation, abdominal pain, nausea, vomiting, and indigestion due to prolonged inhibition of gastric acid HCl secretion.
- **Hypersensitivity** reactions as skin rash and angioedema.
- **Asthenia.**
- **Enzyme inhibition** especially by **omeprazole** for drugs such as diazepam, phenytoin, warfarin.
- Long-term usage leads to gastric enterochromaffin-like cell hyperplasia.

Doses:

Omeprazole: 20-40 mg/day before breakfast orally.

Lansoprazole: 15-30 mg/day before breakfast orally.

Pantoprazole: 40 mg/day before or after breakfast orally or intravenously.

Rabeprazole: 20 mg/day orally.

N.B.: Acid-Suppressing Drugs

HCl secretion by the parietal cells of the stomach needs stimulation of several neurotransmitters as follows (figure 4-17):

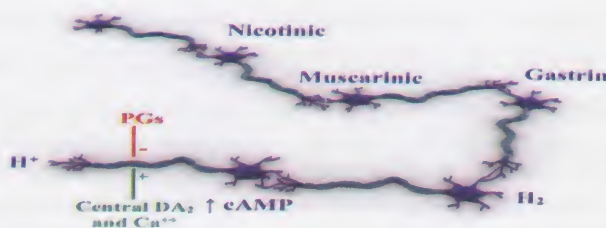


Figure 4-17: Steps of HCl secretion

Acid suppressant drugs include:

- 1- H₂ antagonists.
- 2- Proton pump inhibitors.
- 3- Anticholinergic drugs:

They have the following disadvantages:

- They have a weak effect needing large doses (causing more side effects) due to presence of other mediators that control HCl secretion.
- They decrease the protective mucus (the buffer capacity) more than HCl.
- They delay gastric emptying which may produce aspiration during anesthesia.

For example: - Nonselective: such as atropine and glycopyrrrolate.

- Selective M₁ receptor blockers: pirenzepine and telenzepine.

4- Sulpride (*Colospasmin*, *Coloverin*, *Dogmatil*, or *Duspatalin*): it is selective dopamine DA₂ receptor blocker. It decreases HCl secretion and has antiemetic and antipsychotic actions.

5- Misoprostole (a prostaglandin) (*Cytotec* or *Misotec*).

Antacids

Mechanism of Action:

1- They **neutralize gastric acidity**, increasing the pH of the stomach by providing a base (usually hydroxide, carbonate, bicarbonate, citrate or trisilicate) that reacts with H⁺ to form water; therefore, they produce an immediate action, but increase the gastric volume.

N.B.: Liquid antacids are faster in action than tablets, but chewable tablets can provide a steady effect over a longer period of time.

2- They **inhibit the proteolytic activity of pepsin**; therefore, they prevent erosion and digestion of the base of the ulcer and relieve pain.

3- They **decrease hypermotility**.

Agents:

1- Systemic (Absorbable) Non-Particulate Antacids:

- They produce systemic effects because they are absorbed.
- Advantages: They have a rapid onset, potent, and cheap.
- For example: Sodium bicarbonate (NaHCO₃) (*Fawar fruit* with citric acid and tartaric acid) or citrate.

2- Non-Systemic (Non-Absorbable) Particulate Antacids:

- They produce no systemic effects because they are minimally absorbed.
- Advantages: - They are effective and have a prolonged action.
 - They do not release CO₂, so no distension occurs.
 - They adsorb HCl, pepsin, and bacterial toxins.
 - They produce no acid-base disturbances.
- For example: - Aluminum hydroxide (AlOH) (*Alkasilon* with dimethicone) (*Epicogel* with magnesium hydroxide and dimethicone).
 - Magnesium hydroxide or trisilicate (*Alkomag*, *Mucogel*, *Neogelico* or *Anatacidin* with AlOH).
 - Magnesium aluminum "Magaldrate" (*Acicone* or *Compagene*)
 - Calcium carbonate (*Glycodal* with glycine and dimethicone) (*Rennie* with Mg carbonate).
 - Na⁺ alginate and K⁺ bicarbonate (*Algicab*) or Na⁺ alginate and Na⁺ bicarbonate (*Geviskon*): Na⁺ alginate swells and floats on the gastric contents as a raft which usually prevents gastric reflux.

Uses:

- 1- Immediate pain relief for gastric and duodenal ulcers. ➤

2- Prophylaxis against aspiration before anesthesia e.g., Na citrate 0.3 M solution 15-30 mL orally 15-30 min before induction of anesthesia.

As H₂ antagonists, their routine administration is not recommended but they are given in selected patients who are at risk of aspiration.

In contrast to H₂ antagonists, administration of antacids is effective in increasing the pH of gastric fluid that is present in the stomach at the time of administration (no lag time). This desirable effect, however, is predictably associated with increased gastric fluid volume that does not occur with H₂ antagonists. Nevertheless, withholding antacids because of concern about increasing gastric fluid volume is not warranted.

3- Treatment of GERD and Zollinger-Ellison syndrome.

4- NaHCO₃ is also used - In treatment of acidosis.

- As an alkaline eye lotion.

- In urinary tract infection.

- For production of alkaline urine to treat barbiturate and salicylate toxicities.

- In treatment of uric acid stones.

5- AlOH is also used: - In recurrent phosphate stones as it combines with phosphate in gut and this produces hypophosphatemia.

- In treatment of iron poisoning as it adsorbs iron.

Side Effects:

1- Absorbable antacids (NaHCO₃) cause:

- Alkalinization of urine which precipitates **phosphate stones**.
- Systemic alkalosis due to excess bicarbonate absorption.
- Increased Na⁺ load which may produce harmful effects in cardiac and renal patients.
- Dissolving of mucus in the stomach.
- Rebound action with increased gastric HCl

2- Aluminum containing antacids cause:

- Constipation.
- Accumulation if the patient has renal failure leading to **encephalopathy**.
- Phosphate depletion (except if aluminum phosphate is used) leading to **osteomalacia**.
- Decreased rate of absorption of many drugs as digoxin, phenytoin, warfarin, tetracycline, ketoconazole, phenothiazines, chlorpromazine, cimetidine, ranitidine, anticholinergics, iron preparation, and prednisone.

3- Magnesium containing antacids cause:

- Diarrhea due to increased gut motility.
- Accumulation if the patient has renal failure leading to **cerebral depression**.

4- Calcium containing antacids cause:

- Constipation.
- Rebound hyperacidity.
- Hypercalcemia as 40% of the calcium is absorbed; it may lead to **milk alkali syndrome** with metabolic alkalosis, renal failure, and alkaline urine that causes formation of **phosphate stones**.

5- Non-particulate antacids are preferred to particulate antacids to protect against aspiration pneumonia because:

- If particulate antacids themselves are **aspirated**, they produce lung injury such as **acid pneumonitis**.
- Particulate antacids **do not mix well with gastric contents**.

Gastrointestinal Motility Agents (Prokinetics)

These agents stimulate gastric emptying. They include:

1- Metoclopramide.

2- Cisapride.

3- Erythromycin: it is an antibiotic but it also stimulates gastric emptying. It is a motilin agonist acting on antral enteric neurons.

4- Domperidone (*Motilium*, *Motinorm*, or *Gastromotil*): It acts as a DA₂-receptor blocker. It produces less extrapyramidal effects as it does not cross the blood brain barrier. If injected i.v., it may produce arrhythmias.

Metoclopramide (*Primperan, Plasil, Maxolon, or Meclopram*)

Action:

1- Central Action:

- It has a **dopaminergic (DA₂) receptor blocking action** in the chemoreceptor trigger zone of the central nervous system.
- In high doses; it has a **serotonin (5HT₃) receptor blocking action**.

2- Peripheral Action:

- It **blocks the inhibitory action of dopamine on gut**.
- It has a **cholinergic action** i.e., it sensitizes the gut to acetylcholine and releases ACh from the gastrointestinal cholinergic neurons.

These actions lead to:

- Increased upper gastrointestinal motility that leads to rapid gastric emptying (i.e., prokinetic action) with relaxation of pyloric sphincter.
- Increased tone of lower esophageal sphincter.
- Increased intestinal peristalsis.

It does not affect the secretion of gastric acid or the pH of gastric fluid.

Uses:

- 1- As an **antiemetic** especially for
 - postoperative vomiting.
 - drug induced vomiting.
 - chemo- and radiotherapy vomiting.

It is not effective against motion sickness.

- 2- As a **prophylactic agent** to decrease the risk of aspiration of gastric contents before induction of anesthesia.

- 3- Gastroesophageal reflux disease (**GERD**).

- 4- **Gastric motor failure (gastroparesis)** e.g., - diabetic autonomic neuropathy.
- after vagotomy.

- 5- As an **analgesic** in some conditions associated with **smooth muscle spasm** e.g., renal or biliary colic, uterine cramping due to both anti-dopaminergic and cholinergic action.

- 6- **Endoscopy and barium meals**, as it facilitates passage of the tube into the gastrointestinal tract.

Side Effects:

1- Due to its anti-dopaminergic action:

- **Drowsiness, sedation, dizziness, nervousness, and excitation and convulsions** in children.
- **Extrapyramidal manifestations** such as akathisia, dystonia, torticollis, and facial spasm. It is avoided in patients with Parkinsonism. These are decreased by antihistaminics and benzodiazepines.

2- Endocrine effects:

- Galactorrhea, gynecomastia and menstrual disorders due to increases in aldosterone and prolactin secretion.

- A hypertensive crisis in patients with pheochromocytoma by releasing catecholamines from the tumor.

- 3- **Gastrointestinal effects:** diarrhea (can be decreased by dexamethasone), abdominal cramping on rapid i.v. injections; therefore, it is avoided in intestinal obstruction.

Drug Interactions:

1- Due to its prokinetic action:

- It decreases the absorption of cimetidine if the latter is taken orally (via the stomach).
- It increases the absorption of aspirin, paracetamol, tetracycline, and levodopa (via the small intestine).

2- Due to its anti-dopaminergic action:

- It potentiates phenothiazines and butyrophenones increasing their extrapyramidal manifestations.
- It potentiates thiopental decreasing its dose of induction of anesthesia.

Metoclopramide does not reverse the effects of low-dose dopamine infusion on the renal vasculature.

3- Due to its cholinergic action:

- It antagonizes the anticholinergic drugs as atropine and they block metoclopramide action.

Pharmacokinetics:

Onset of Action: 30-60 min after oral intake.

3-6 min after i.v. or i.m. administration.

Dose:

- It is taken orally, i.m., slowly i.v., or by rectal route.

- The dose is 0.1-0.25 mg/kg/8 hours. 10-20 mg is the usual adult dose. Recently, some studies suggest that this dose is not effective and a recent dose of 25 mg is considered the minimally effective dose and 50 mg may even be better for 24 hour coverage.
- Higher doses 1-2 mg/kg as an antiemetic during chemotherapy.

Antiemetics

Physiology of Vomiting

Physiology of vomiting is discussed in the chapter of "Miscellaneous Problems in Anesthesia & Intensive Care".

Therapeutic Emesis

Indication: It is indicated in case of poisoning to evacuate gastric contents.

Contraindications:

- Unconscious patients to avoid aspiration.
- In case of swallowing corrosive materials.

Agents and Techniques:

1- Mechanical Stimulation of the Throat.

2- Syrup Ipecac:

It induces vomiting within 20 minutes.

Doses: 30 mL for adults

10-15 mL for children.

3- Apomorphine:

It is a parenteral opioid acting as an emetic agent as it stimulates the chemoreceptor trigger zone. It is faster in onset than ipecac. Naloxone should be available to reverse neurological and respiratory depression.

N.B.: Hypertonic Salt Solution:

It was used as an emetic agent, but it is obsolete nowadays as it may cause fatal hypernatremia.

Antiemetics

Drug	Mechanism of Action	Choice of Use
A) Dopamine antagonists: 1- Phenothiazines as: • Chlorpromazine (<i>Largactil</i>). • Promethazine (<i>Phenergan</i>). • Prochlorperazine. 2- Butyrophenones as: haloperidol (1 mg) or droperidol (0.625 or 1.25 mg). 3- Metoclopramide. 4- Domperidone. 5- Sulpride.	• They block dopamine receptors (DA ₂) in the chemoreceptor trigger zone. • Both metoclopramide and domperidone have peripheral actions also.	• Postoperative vomiting. • Drug-induced vomiting. • Radio- and chemotherapy vomiting. • Vomiting of pregnancy by metoclopramide and Promethazine.
B) Anticholinergic agents: e.g., • Hyoscine (0.3-0.6 mg/8 hours orally or trans-dermal patch 2 hours before surgery). C) Antihistaminics (H₁ blockers): e.g., • Dimenhydrinate (<i>Dramamine</i>). • Cyclizine. • Meclozine. • Hydroxyzine. • Diphenhydramine.	• They prevent stimulation of the vomiting center by impulses from the vestibular apparatus and the eyes.	• Vestibular vomiting. • Motion sickness prophylaxis. - Anticholinergics for short journeys. - Antihistaminics for long journeys.
D) Serotonin (5HT₃) antagonists: e.g. • Ondansetron. • Granisetron. • Dolasetron. • Tropisetron. • Palonosetron (the most recent).	• They block serotonin receptors in the vomiting center and chemoreceptor trigger zone. • They have a peripheral action in the gastrointestinal tract.	• Postoperative vomiting by ondansetron. • Chemo- and radio-therapy vomiting by granisetron.

E) Glucocorticoids: e.g.,

- Dexamethasone (150 µg/kg up to 8 mg).
- Methyl prednisone.

In large doses especially with phenothiazines and metoclopramide.

- Chemotherapy vomiting.

F) Other drugs:

1- Cannabinoids e.g., **nabilone** or **dronabinol** is a synthetic cannabinoid with potent antiemetic action. It may cause drowsiness, dry mouth, mood changes, and postural hypotension.

2- Benzodiazepines e.g., **lorazepam**: are used as sedatives and antiemetics due to psychogenic and anticipatory nausea and vomiting. They potentiate the other dopaminergic antagonists and decrease their extrapyramidal side effects.

3- Vitamin B6 (Pyridoxine): it produces antiemetic action due to affection of GABA-glutamate balance. It is safe and used mainly in **vomiting due to pregnancy**.

4- Neurokinin-1 (NK₁)-Receptor Antagonist: Aprepitant is the most recent antiemetic drug. It is the only NK₁ receptor antagonist currently approved by the food and drug administration for prophylaxis in postoperative nausea and vomiting. It is effective in chemotherapy-induced nausea and vomiting. The NK₁ receptors are located in the area postrema and vomiting center and thought to play an important role in emesis. Aprepitant is available in an oral capsule at 40 mg to be administered between 1 and 3 hours before surgery. It has a long half-life of about 48 hours. It is more effective than ondansetron.

Serotonin (5-Hydroxytryptamine "5-HT") Physiology

Synthesis: Synthesis of serotonin is discussed in figure 4-18.

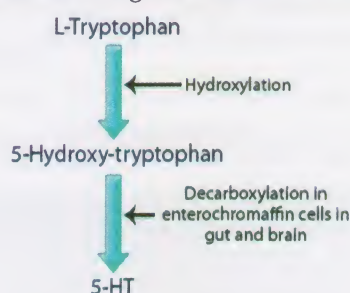


Figure 4-18: Synthesis of serotonin

• 5-HT is metabolized by MAO enzyme to 5-hydroxy indole-acetic acid (5-HIAA) which is excreted in the urine. Its excretion is increased in the urine in carcinoid tumors, on reserpine intake, or on food intake which is rich in 5-HT such as bananas, tomatoes, plums and nuts.

Actions:

There are at least 7 receptor types with multiple subtypes

	5-HT ₁ -Receptors	5-HT ₂ -Receptors	5-HT ₃ -Receptors
Mechanism	<ul style="list-style-type: none"> • 5-HT_{1A, B} receptors act via Gi and Gs proteins. • 5-HT_{1C} receptors act via Gq protein. 	<ul style="list-style-type: none"> • 5-HT₂ receptors act via Gq protein. 	<ul style="list-style-type: none"> • 5-HT₃ act directly by linking to membrane ion channels.
Actions	<ul style="list-style-type: none"> • Anxiety. • Vasodilatation of skeletal and coronary vessels leading to hypotension. • Vasoconstriction of meningeal vessels. 	<ul style="list-style-type: none"> • Increase platelet aggregation. • Vasoconstriction of renal, pulmonary, and mesenteric vessels. • Contraction of smooth muscles of bronchi, gastrointestinal tract, and uterus. Bronchospasm is a prominent feature of carcinoid tumor. 	<ul style="list-style-type: none"> • Stimulation of baroreceptors and chemoreceptors in the coronary vessels (Vonbezold-Jarisch reflex) resulting in a decrease in heart rate and blood pressure and in apnea. • Vomiting. • Pain and itching.
Agonists	<ul style="list-style-type: none"> • Sumatriptan is used for migraine. • Buspiron and ipsapirone are used for anxiety. • Flesinoxan and urapidil decrease central sympathetic 	<ul style="list-style-type: none"> • α-methyl 5-HT. • Ergot alkaloids as LSD₂₅ 	<ul style="list-style-type: none"> • α-methyl 5-HT.

	outflow and increase vagal tone causing a decrease in heart rate and blood pressure. they are 5-HT _{1A} agonists.		
Antagonists	<ul style="list-style-type: none"> • Spiperon 	<ul style="list-style-type: none"> • Ketanserin and cinanserin (they are used as antihypertensive agents and in bronchial asthma). • Cyproheptadine: it has also antihistaminic and antimuscarinic actions (used as a sedative, as an appetizer, and in urticaria). • Methysergide. • Pizotifen (<i>Mosegor</i>) and Ketotifen: they stimulate appetite. • Clozapine. 	<ul style="list-style-type: none"> • Ondansetron. • Granisetron. • Dolasetron. • Tropisetron. • Palonosetron.

• 5-HT₄ receptors mediate secretion and peristalsis in gastrointestinal tract.

5-HT₆ and 5-HT₇ receptors are located primarily in the limbic system as they appear to play a role in depression.

• **Cardiac actions:** - Weak inotropic and chronotropic actions.

- **Triphasic response on arterial blood pressure:**

- Initial decrease in blood pressure because serotonin stimulates chemoreceptors in coronary vessels resulting in a decrease in heart rate and blood pressure and in apnea (Vonbezold-Jarisch reflex).
- Then an increase in blood pressure due to direct vasoconstriction.
- Finally a decrease in blood pressure due to vasodilatation of skeletal vessels and histamine release.

• **Respiratory actions:**

A biphasic response occurs:

- Initial inhibition due to Vonbezold-Jarisch reflex.
- Then stimulation due to stimulation of chemoreceptors of the carotid body.

5-HT₃ Receptor Antagonists

Mechanism of Action:

They selectively block 5-HT₃ receptors either:

- Peripherally; in the abdominal vagal afferents.
- Centrally; in the chemoreceptor trigger zone of area postrema and the nucleus tractus solitarius.

They do not affect gastrointestinal motility or lower esophageal sphincter tone.

Uses: They are used as antiemetics for both prophylaxis and treatment especially in postoperative nausea and vomiting.

Side Effects:

They are very few even in large doses (no sedation or extrapyramidal signs, or respiratory depression).

- Headache is the most common.
- Slight prolongation of the QT interval especially with dolasetron, but no arrhythmia occurs.

Pharmacokinetics

Ondansetron is metabolized mainly in the **liver**, so its dose should be decreased in liver failure.

Agents:

- Ondansetron (*Zofran*, *Danofran*, *Emerest*, or *Danset*): orally or i.v. **4-8 mg** at induction of anesthesia or at the end of surgery, then can be repeated **every 4-8 hours**.
- Granisetron (*Kytril*, *G-Setron*, or *Granytril*): orally or i.v. 1 mg.
- Dolasetron (*Anzemet*): orally 100 mg and i.v. 12.5 mg.
- Tropisetron (*Navoban*).
- Palonosetron: it is the most recent with elimination $t_{1/2}$ about 40 hours due to its high affinity to receptors. It is the only serotonin antagonist on the market that has shown effectiveness for delayed chemotherapy-induced nausea and vomiting beside its effect for postoperative nausea and vomiting.

HEMATOLOGICAL DRUGS

A) Antithrombotic Therapy:

They are drugs that prevent formation of thrombus (clot formation) and its embolization to distant sites. They include:

- Anti-platelets (anti-thrombotics).
- Anticoagulants.
- Fibrinolytics (thrombolytics).

B) Coagulant therapy

They are drugs that enhance clot formation to prevent excessive bleeding e.g., during surgical procedures. They include:

- Anti-plasmins (anti-fibrinolytics or anti-thrombolytics).
- Vitamin K.
- Protamine.
- Activated factor VII (F VIIa)

Anti-Platelets (Anti-Thrombotics)

Physiological Considerations of Platelet Action

Platelets are responsible for formation a **platelet plug** (i.e., the **primary hemostasis**) through several mechanisms which include:

- **Platelet adhesion:** It is the affinity of platelets to non-platelet surfaces.
- **Release reactions.**
- **Platelet aggregation:** It is the affinity of platelets to one another.

Then reinforcement of platelet aggregation occurs with fibrin strands leading to formation of a hemostatic plug (figure 4-20).

Classifications of Anti-Platelets (Anti-Thrombotics)

Uses: They are used either alone or in combination with anticoagulants for prevention and treatment of arterial thrombosis e.g., in unstable angina, suspected acute myocardial infarction, nonfatal stroke, transient ischemic attacks, peripheral vascular diseases, or in those undergoing vascular surgeries such as carotid artery surgeries.

1- Drugs Inhibiting the Arachidonic Acid Pathway:

a- Cyclo-Oxygenase Inhibitors: Non-steroidal anti-inflammatory drugs (NSAIDs)

Mechanism of Action

It is described in figure 4-19.

- **Aspirin** (acetylsalicylic acid) **irreversibly** inhibits cyclo-oxygenase enzyme (COX), which cannot be re-synthesized by platelets because they have no nucleus.
- **Other NSAIDs** such as indomethacin, indobufen, flurbiprofen and triflusal **reversibly** inhibit the enzyme.

The anti-platelet dose is very small as compared with the analgesic dose; it is 75 mg/ day.

For routes and side effects, see the chapter of "Pain Management".

b- Thromboxane Synthetase Inhibitors:

- Propranolol.
- Dazoxiben.

2- Selective ADP Receptor (Especially P₂Y₁₂ Type) Antagonists:

	Ticlopidine (Ticlid or Ticlopidine)	Clopidogrel (Plavix, Myogrel, or Stroka)
Absorption (oral)	90%	Rapid
Half-life	24-36 hours after single dose 4-5 days after 14 days of therapy because it has a cumulative effect.	7.7 hours after a single 75-mg dose. Several days with repeated doses.
Active metabolites	Yes	Yes
Onset of antithrombotic action	Delayed up to 2 weeks	2 hours after single 400 mg dose. 1 day after 50-100 mg daily doses.

Recovery of platelet function after discontinuing drug	7 days Regional anesthesia can be done 7-14 days after its cessation.	7 days Regional anesthesia can be done 7 days after its cessation.
Clinical use	The main indication nowadays is cerebral ischemia with aspirin resistance or intolerance	All the uses as above. It can be combined with aspirin after coronary artery stent placement.
Side effects	<ul style="list-style-type: none"> • Neutropenia, thrombocytopenia, and aplastic anemia especially in the first 3 months, so monitoring of blood count is mandatory during this period. • Rash. • Diarrhea. • Reversible liver dysfunction. 	<ul style="list-style-type: none"> • Neutropenia and thrombocytopenia. • Rash. • Diarrhea. • Gastrointestinal bleeding.
Recommended dose	250 mg orally/12 hours	300 mg loading dose 75 mg orally/day as a maintenance dose.
Antidote	<ul style="list-style-type: none"> • Platelet infusion. • Methylprednisolone 20 mg i.v. 	

3- Glycoprotein IIb/IIIa Receptor Antagonists or Platelet Fibrinogen Receptor Blockers (Integrin Complex Blocker):

Agents and Mechanisms

a- Reversible Competitive Receptor Antagonists:

- **Eptifibatide** (*Integrilin*): it is a synthetic heptapeptide similar to that found in snake venom from *Sistrurus m barbouri*. Its half-life is 2.5 hours
- **Tirofiban** (*Aggrastat*): it is a non-peptide. Its half-life is 1.5-2.5 hours.

b- Irreversible Non-Competitive Receptor Antagonists:

- **Abciximab** (*Reopro*): It is a recombinant humanized monoclonal antibody against the integrin complex. Its half-life is 12-24 hours. It is not reversed by platelet transfusion due to persistence of the antibodies. In contrast to aspirin, ticlopidine, and clopidogrel, these effects are rapidly reversible after discontinuation of the drug (4-8 hour for eptifibatide and tirofiban, and 48 hours for abciximab).

Side Effects:

- Bleeding tendency and thrombocytopenia.

4- Drugs Increasing Intra-platelet cAMP and/or Activating Adenosine Receptors:

a) Drugs Inhibiting Adenosine Deaminase and/or Phosphodiesterase Enzyme:

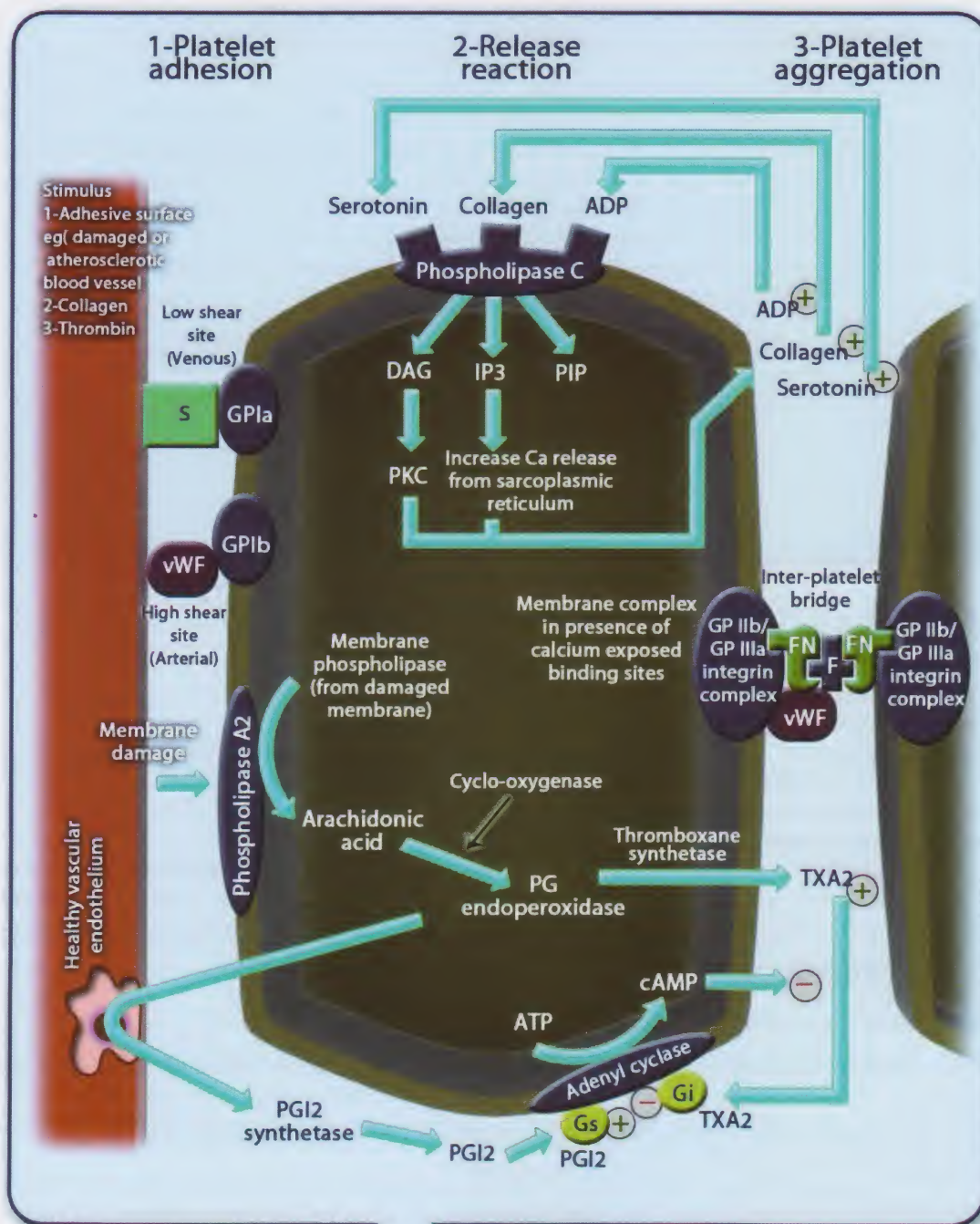
- Dipyridamole (*Persantin* or *Persantin plus* with aspirin).

b) Thromboxane (TXA₂) Receptor Antagonists:

- Vapiprost.
- Trimetoquinol.

c) Prostanoids or Prostaglandins (PGs):

- PGI₂ (Prostacyclin) and its analogues as iloprost and beraprost.
- PGE₁ as alprostadil or epoprostanil.
- PG releaser as defibrotide.



GP = Glycoproteins
vWF = Von Willebrand factor
TXA2 = Thromboxane A2
IP3 = Inositol triphosphate
DAG = Diacyl glycerol
PKC = Protein kinase C
PIP2 = Phosphatidyl inositol diphosphate
FN = Fibronectin
F = Fibrinogen
S = subendothelial collagen

Figure 4-19: Formation of a platelet plug

Anticoagulants

Physiological Considerations:

- After formation of the primary clot, the firm clot (coagulation) is formed by the help of coagulation factors.
 - The rigid division of the coagulation cascade into an extrinsic and intrinsic system has lost absolute validity due to crossover of many factors for example,
 - Factor VIIa can activate factor IX.
 - Factors IXa, Xa, XIIa, and thrombin can activate factor VII.
 - Effective hemostasis requires both systems to function together.
- For the coagulation cascade see later chapter of anesthesia and blood diseases.

N.B.:

Serine proteases include both **thrombin (induces formation of clot)** and **plasmin (induces lysis of clots)**. Anti-thrombin III is a naturally occurring protease inhibitor. It inhibits thrombin and other serine proteases.

Classification of Anticoagulants

I) Injectable Anticoagulants:

1- Indirect Thrombin Inhibitors:

- Heparin.
- Low molecular weight heparins (LMWHs).
- Pentasaccharide analogues.
- Heparinoids.

2- Direct Serine Protease Inhibitors:

➤ Selective: Direct Thrombin Inhibitors:

- r-Hirudin.
- Bivali-rudin.
- Lepi-rudin.

➤ Non-Selective: Direct Serine Protease Inhibitors:

- Cabexate.
- Urinastatin.

3- Selective Factor Xa Inhibitors:

- Antistatin.

4- Direct Fibrinogen Depletors (Defibrinating Agents):

- Ancrod.

5- Others:

- Activated protein C.
- Sodium citrate.
- Anti-thrombin-III concentrate.
- Thrombo-modulin.

II) Oral Anticoagulants:

- Coumarin derivatives as dicumarol and warfarin.
- Indanedione derivatives as phenindione (Dindevan) and diphenadione and anisindione.

Indirect Thrombin Inhibitors

	Un-Fractionated Heparin (UFH)	Lower-Molecular-Weight Heparins (LMWHs)
Chemical structure	<ul style="list-style-type: none"> • It is derived from porcine intestine or bovine lung. • It is a mixture of heterogeneous higher-sized molecules (MW 3000-33,000). • It contains a long polysaccharide chain (18 saccharides) in a pentasaccharide portion. 	<ul style="list-style-type: none"> • They are derived by depolymerization of UFH by chemical or enzymatic means. • It is a mixture of lower MW molecules (100-10,000). • It is formed of the pentasaccharide but without the long polysaccharide chain.

Action	<p>1- Anticoagulant action: (it affects the intrinsic pathway).</p> <ul style="list-style-type: none"> • It activates and binds to anti-thrombin III forming a complex which inhibits activated thrombin (IIa) (done by the pentasaccharide portion of the heparin; the long polysaccharide chain). • It also inhibits other coagulation factors as, IXa, Xa (mainly), XIa, and XIIa and this is mediated by antithrombin (not done by the pentasaccharide portion). • At high concentration, it also activates heparin cofactor II (another anti-thrombin) which forms irreversible complex with thrombin resulting in inactivation of activated coagulation factors and thrombin. <p>2- Lipemic clearing action: UFH activates lipoprotein lipase decreasing triglycerides and increasing free fatty acids.</p> <p>3- Mild vasodilatation: of collateral circulation leading to canalization of thrombus.</p>	<p>1- Anticoagulant action:</p> <ul style="list-style-type: none"> • As UFH, LMWH accelerates anti-thrombin-mediated inactivation of factor Xa, but unlike UFH, LMWH does not inactivate thrombin (IIa) or form complex with it because it lacks the long polysaccharide chain of the pentasaccharide portion and contains instead short polysaccharide chain which does not reach the IIa-binding sites.
Pharmacokinetics	<ul style="list-style-type: none"> • Not absorbed orally due to large MW. • Short duration: 4 hours (due to first order kinetics). • Rapid onset: 15 minutes. • Plasma half-life: 1-2.5 hours. • Metabolized by heparinase enzyme in the liver producing inactive metabolites that are excreted in urine. It also binds to endothelial cells where it is neutralized by platelet factor 4 and taken up by macrophages and desulfated. • Does not cross the placental barrier or enter the milk; therefore, it is of choice during pregnancy and lactation (it is also not teratogenic). 	<ul style="list-style-type: none"> • Longer duration 12-24 hours. • Plasma half-life: 2-6 hours. • Excreted by the kidneys, so its action is prolonged in renal failure.
Side effects	<p>1- Hemorrhage and bleeding tendency especially with the intermittent doses more than continuous infusion.</p> <p>2- Heparin-induced thrombocytopenia (by the high-molecular-weight fraction) which is of two types (type I and type II), see chapter of "anesthesia for cardiac surgery".</p> <p>3- Allergic reactions (by the high-molecular-weight fraction).</p> <p>4- Osteoporosis because heparin binds to osteoblasts that release factors that stimulate osteoclasts.</p> <p>5- Alopecia and skin necrosis.</p> <p>6- Transient elevation of liver enzymes.</p> <p>7- Hyperkalemia.</p> <p>8- Hypo-aldosteronism.</p>	<p>They are similar to UFH except thrombocytopenia, allergic reactions, and osteoporosis which are very rare with LMWH.</p>
Doses	<p>Heparin sodium or heparin calcium (<i>Heparin, Cal-Heparin, or Calciparine</i>)</p> <ul style="list-style-type: none"> • Ampoule: 5000 IU (50 mg) • Vial: 25000 (250 mg) <p>1 mg = 100 units</p> <p>It is used i.v. or subcutaneously, but not i.m. due to hematoma formation.</p>	<ul style="list-style-type: none"> • Enoxaparin (<i>Clexane</i>): 1 mg of enoxaparin = 100 anti-factor Xa units. In deep venous thrombosis prophylaxis, in USA: 30 mg/12 hours subcutaneously in Europe 40 mg/24 hours subcutaneously • Nadroparin (<i>Fragmin, or Fraxiparine</i>). • Tinzaparin (<i>Innohep anti-Xa</i>) • Dalteparin. <p>Dose: 0.5-1.0 unit/mL.</p>
Control	<ul style="list-style-type: none"> • Control times (they should not be more than double the normal values) - Clotting time (10-12 minutes). - Thrombin time (30-45 seconds): it is the most sensitive as it is prolonged even if a very small dose of heparin is given. - Activated partial thromboplastin time (aPTT) (45-70 seconds): is intermediate in sensitivity. It is the most commonly used monitor of heparin's effect. - Prothrombin time (PT): is the least sensitive measure of 	<ul style="list-style-type: none"> • It does not require laboratory monitoring by aPTT as aPTT is not prolonged. • It gives more predictable response; therefore, it can be used for outpatients. • In obese patients and

	heparin's effect. It remains normal except with large doses of heparin. <ul style="list-style-type: none"> • Platelet count should be monitored every 1-2 days. Therefore, it should be used for inpatients only. 	renal impairment, monitoring of anti-factor Xa activity is needed.
Antidote	<ul style="list-style-type: none"> • Protamine sulfate (alkaline); every 1 mg neutralizes 100 IU of acidic heparin (i.e., 50 mg protamine for 5000 IU heparin) over 10 minutes. 	<ul style="list-style-type: none"> • Protamine sulfate is much less effective in reversing the effect of LMWH than UFH, but if serious bleeding occurs, protamine sulfate 1 mg per 100 anti-factor Xa units of LMWH is given (1 mg of enoxaparin = 100 anti-factor Xa units). • Activated factor VII may be used.
Remarks	Heparin resistance is due to: <ul style="list-style-type: none"> • The presence of elevated factor VIII or fibrinogen levels as excess fibrin binds to thrombin and protects it from heparin. • Increased heparin-binding protein as plasma proteins bind and neutralize heparin. • Increased heparin clearance in endothelial cells by platelet factor 4 produced by the platelets. • Anti-thrombin III deficiency (hereditary or acquired). 	

Indications of Heparin:

- 1- Deep venous thrombosis.
- 2- Pulmonary embolism.
- 3- Prophylaxis of myocardial infarction.
- 4- Mural thrombus after myocardial infarction.
- 5- Extracorporeal circulations as during cardiac and vascular surgeries and hemodialysis.
- 6- Disseminated intravascular coagulopathy.
- 7- Acute arterial occlusion.
- 8- Before cardioversion in atrial fibrillation (if no mural thrombus is detected by trans-esophageal echocardiography).
- 9- Placental infarctions to treat fetal growth retardation during pregnancy.
- 10- During interruption of oral anticoagulant therapy such as during invasive procedures and surgeries until oral anticoagulant is reused.
- 11- Fat embolism (by UFH).

Pentasaccharide Analogues

These drugs are synthetic analogues of the pentasaccharide sequence and do not contain the long polysaccharide chain; therefore, no antithrombin III/drug complex occurs and no inhibition of thrombin (factor IIa) takes place. They are selective factor Xa inhibitors.

Action:

They form a complex with antithrombin that binds to and inhibits factor Xa (mainly) and factor IIa (to a lesser extent).

Fondaparinux (FONDA, Arixtra)

It is the only agent clinically available. It is similar to heparin except that:

- It is excreted by the kidneys, so should be avoided in patients with renal impairment.
- It does not cause thrombocytopenia because it does not bind to platelet factor 4 and it is synthetic and not derived from animal sources; therefore, no antibodies are produced against the platelets. Non-antibody-mediated thrombocytopenia still may occur which should be closely monitored.
- There is no antidote, but recombinant factor VII may be used to treat excessive bleeding.
- Dose: 2.5 mg subcutaneously/24 hours. The first dose is given 6-8 hours after completion of surgery.

Heparinoids

These are low-molecular-weight glycosaminoglycuronans derived from porcine intestinal mucosa.

Danaparoid

It is the only agent clinically available. It is formed of a mixture of:

- Heparan sulfate: has a high affinity for antithrombin and is responsible for the major anticoagulant effect of danaparoid.
- Dermatan sulfate: mediates development of heparin cofactor II-thrombin complexes and contributes to the anticoagulant effect.
- and - Chondroitin sulfate.

It is similar to LMWH except that:

- It has a higher action as anti-factor Xa than LMWH and has also minimal effects on aPTT, PT, and thrombin time.
- It has fewer effects on platelets than heparin.
- It is mainly used in heparin-induced thrombocytopenia.
- Like LMWH and UFH, it does not cross the placenta, so it can be used during pregnancy.
- Dose: 2250 units i.v. bolus followed by 400 units/hour for 4 hours, then 300 units/hour for the next 4 hours, then 150-250 units/hour.

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Direct Thrombin Inhibitors

These drugs inhibit thrombin directly (both clot-bound thrombin and fluid-phase thrombin). Unlike heparin, they do not depend on anti-thrombin III in their anticoagulant effects.

They also do not bind to plasma proteins and are not neutralized by platelet factor 4; therefore, they have very few bleeding complications and do not produce thrombocytopenia.

They are used mainly, instead of heparin, in heparin-induced thrombocytopenia.

There is no available antidote for them.

1- r-Hirudin: (*Thrombexx*)

- It is a coagulation inhibitor isolated from the **salivary glands of the medicinal leech**. It is now synthesized by recombinant technology (r).
- It is mainly excreted **by the kidneys**; therefore, its dose should be decreased in patients with renal impairment.
- Dose: 0.25 mg/kg i.v. followed by infusion.
- Monitoring: by ecarin clotting time.

2- Bivalirudin:

- It is a synthetic derivative of hirudin.
- Its active part is cleaved by the thrombin itself, so it **does not depend on organ elimination**.
- Its $t_{1/2}$ = 24 min.
- Monitoring by ecarin clotting time.

3- Lepirudin:

- It is a recombinant hirudin derivative.
- It is mainly excreted **by the kidneys**, therefore; its dose should be decreased (or completely not used) in patients with renal impairment.
- Its $t_{1/2}$ = 40-120 minutes
- Dose: 0.4 mg/kg (up to 44 mg) i.v. bolus followed by 0.15 mg/kg/hour.

4- Argatroban

- It is a carboxylic acid derivative.
- It is metabolized by the liver; therefore, it can be used in patients with renal impairment.

Direct Fibrinogen Depleters (Defibrinating Agents):

Ancrod

- It is an enzyme derived from the Malayan pit viper.
- It is a defibrinogenating agent as it cleaves fibrinogen and causes hypofibrinogenemia.
- It is used mainly in heparin-induced thrombocytopenia as it does not affect platelets.
- Its activity is monitored by plasma fibrinogen concentration.

- Dose: 1 unit/kg i.v. infusion over 8-12 hours, followed by daily maintenance doses adjusted according to the level of fibrinogen.
- An antivenom is available as an antidote to reverse its effect. Cryoprecipitate is used to elevate fibrinogen levels if excessive bleeding occurs.

Sodium Citrate

Action: it chelates ionized calcium.

Uses:

It is used for extracorporeal circulation where sodium citrate has advantages over heparin in that: - It has no known anti-platelet activity.

- It is readily filtered by a hemofilter (reducing its systemic anticoagulation).
- It is neutralized when it returns to central venous blood.

Doses: I.v. infusion at 5 mmol/liter of extracorporeal blood flow.

Side Effects:

- Hypocalcemia
- Hypernatremia.

Activated Protein C (Drotrecogin α -Activated) (Xigris)

It is a recombinant activated form of the endogenous anticoagulant protein C.

Actions:

1- Anticoagulant Action:

• Early in the septic process, coagulation is activated by tissue factor, exposed on the surface of endothelial cells after stimulation with endotoxins or pro-inflammatory mediators including interleukin-1 (IL-1), tumor necrosis factor (TNF) and platelet-activating factor (PAF). The end result is the conversion of prothrombin to thrombin. **Thrombin** is an important pro-coagulant protein and **has also an anticoagulant action** as it binds to thrombo-modulin forming **thrombin/thrombo-modulin complex** which **activates protein C**.

- The activated protein C produces its anticoagulant function by:
 - degradation of factors Va and VIIIa,
 - inhibition of thrombin generation.
- The activated protein C also produces fibrinolysis by inhibiting plasminogen activator inhibitors.

2- Anti-Inflammatory Action:

- Activated protein C has **indirect** anti-inflammatory effects related to **its inhibition of thrombin**.
- It also has **direct** anti-inflammatory effects, including:
 - **reducing nuclear translocation of nuclear factor-kB** with a resultant fall in synthesis of cytokines
- and - reducing leukocytes adhesion and activation.

3- Anti-Apoptotic Action:

It is mediated by the interaction between activated protein C, the endothelial cell protein C receptors, and protease-activated receptors.

Uses:

It decreases morbidity and mortality in patients with sepsis.

Side Effects:

- 1- Expensive drug (about 8000 \$ for a 4-day regimen in a 70-kg patient).
- 2- Bleeding tendency e.g., intracerebral hemorrhage.

It is recommended that treatment with activated protein C should be **stopped 2 hours prior to any surgical or invasive procedure** and recommended 2 (for minor procedures e.g., chest tube insertion, central venous catheterization...etc) to 12 (for major surgeries) **hours after the procedure is completed**.

Contraindications:

A) Absolute:

- Active internal bleeding.
- Trauma with an increased risk of life threatening bleeding (e.g., to the liver, spleen...etc).
- Central nervous factors:
 - Presence of an epidural catheter.
 - Recent hemorrhagic stroke (within 3 months).
 - Recent central nervous system surgery or head trauma (within 2 months).
 - Intracranial mass or evidence of cerebral herniation.

B) Relative:

- Abnormal coagulation: - Bleeding diathesis.
 - Platelet count $< 30,000 \times 10^6/L$.
 - Very prolonged INR > 3.0 .
 - Full dose heparin therapy.
 - Recent thrombolytic or glycoprotein IIb/IIIa therapy.
- Significant risk of bleeding: - Polytrauma.
 - Intracranial arterio-venous malformation or aneurysm.
 - Active gastric ulcer or esophageal varices.
- Recent ischemic stroke (within 3 months).

Doses:

For sepsis, an i.v. infusion of $24 \mu g/kg/hour$ is given for 96 hours.

Oral Anticoagulants

Mechanism of Action:

- They have an **indirect action** as they inhibit both **vitamin K epoxide reductase** and **vitamin K reductase enzyme** (because oral anticoagulants are similar to vitamin K in structure); therefore, they prevent production of the active form of vitamin K. Therefore, there is no γ -carboxylation of **factors II, VII, IX, and X** (vitamin K dependent factors) and there is no production of new factors. Depletion of these factors occurs within 2-5 days.
- An anticoagulation effect occurs within 24 hours of instituting warfarin therapy as a result of the inhibition of the production of factor VII which has a short half-life of 6-7 hours. The peak anticoagulation effect is delayed for 72-96 hours due to the longer plasma half-life of these factors (II, IX, and X).
- Protein C and S (natural anticoagulant proteins) are also dependent on vitamin K in their synthesis, so their amounts are also decreased. Protein C also has a relatively short half-life, like factor VII. Therefore, slight hypercoagulation may occur at the onset of therapy (during the first 24-48 hours), but the anticoagulant action of the oral anticoagulant predominates later on.

Pharmacokinetics

They are well absorbed orally and are highly bound to plasma proteins (97% for plasma proteins).

They are mainly metabolized in the liver.

They can pass through placenta and enter the milk.

Onset: is delayed to 2-5 days until the already circulating vitamin K dependent factors are metabolized. Therefore, if rapid anticoagulation is needed, heparin (UFH or LMWH) should be given for at least 4 days at the start of warfarin therapy until the international normalization ratio (INR) becomes within the therapeutic range.

Duration is long 2-7 days as this period is needed until new factors are formed.

Uses:

The same indications, as heparin, except during pregnancy and liver diseases.

Side Effects

- 1- **Hemorrhage and bleeding tendency** especially in old age > 75 years and if aspirin or other anti-platelet therapy is taken e.g., cerebral, gastrointestinal or renal bleeding.
 - 2- **Agranulocytosis.**
 - 3- **Gastrointestinal upset.**
 - 4- **Liver dysfunction.**
 - 5- **Allergy as drug eruption** and alopecia.
 - 6- **Warfarin skin necrosis** especially in the first 2-7 days after initiation of the therapy due to extensive thrombosis of venules and capillaries of subcutaneous fat, particularly in the lower extremities, buttocks, or breast. This appears to be most common in patients who have an inherited or acquired deficiency of protein C or protein S. Those patients should receive simultaneous heparin for the first 5 days of warfarin therapy.
 - 7- **Teratogenicity** especially if it is used in the first trimester.
 - 8- **Fetal hemorrhage** because it crosses the placenta especially near term.
- Fro 7 and 8, warfarin is contraindicated during pregnancy in the first trimester and near term.
- 9- **On withdrawal, thrombotic complications** occur.

Drug Interaction**A) They are potentiated by:**

- 1- Drugs which decrease vitamin K:
 - Decreased synthesis by broad spectrum oral antibiotics.
 - Decreased absorption by paraffin oil.
- 2- Drugs highly bound to plasma proteins as NSAIDs, phenytoin, and amiodarone.
- 3- Enzyme inhibitors as chloramphenicol, cimetidine, and allopurinol.
- 4- Drugs decreasing coagulation as anabolic steroids, dextrans, and salicylates.

B) They are antagonized by:

- 1- Cholestyramine which binds them in gut.
- 2- Enzyme inducers as barbiturates.
- 3- Drugs which increase coagulant factors as estrogen and oral contraceptive pills.

Antidote Reversal of anticoagulated patients (on oral anticoagulants) before surgery:**1) Phytomenadione (vitamin K₁)** (*Konakion, AdcoKion, Amri-K, C & K, Haemokion, Phytovit, or Cona-adione*):

- Dose: 5 mg i.v. is usually given, but 0.5 - 1.0 mg i.v. is sufficient to return INR to its target within 24 hours.

• Duration of reversal: **6-24 hours** (it can not be hastened by a larger dose). If **excessive vitamin K₁** is given, it may render the patient **refractory** to further warfarinization for days or weeks.

N.B.: Acetaminaphetone, menadiol, and phytomenadione are all names for vitamin K.

2) If a more rapid reverse is required (for emergency surgery):

- **Fresh frozen plasma (FFP)**: up to 1 liter (5 units), group "O" FFP is used.
- **Vitamin K dependent factor concentrates**: containing factor II, VII, IX, and X at a dose of 50 µg/kg.

It is unwise to fully reverse anticoagulation in patients with prosthetic heart valves. A cardiologist advice is required.

- **Purified prothrombin complex** (*Octaplex or Beriplex*) 50 µg/kg, will correct INR within 20-30 minutes.

Control: At first, monitoring is done more frequent on daily basis then 3/week and after stability monitoring is done once/month.

- **Prothrombin time (PT)** should be 1.3-2.5 times control (PT ratio).

aPTT is slightly affected; therefore, it cannot be used for assessment.

• International normalization ratio (INR):

- Its normal value = 1-1.2
- The therapeutic range for Atrial fibrillation, pulmonary embolism, and tissue heart valve = 2-3, while the therapeutic range for mechanical heart valves = 3-4.5.
- It is more reliable in assessing warfarin therapy because INR avoids the variation of the results due to the marked inter-laboratory variability in the sensitivity of the thromboplastin reagents used in the PT assay. INR results are produced by comparing the PT ratio obtained by the laboratory thromboplastin with an international reference thromboplastin to get accurate results.

Factors affecting the response of oral anticoagulants resulting in response variability:**Factors increasing the action and response of oral anticoagulants**

- Decreased dietary vitamin K.
- Diarrhea.
- Fever.
- Hepatic failure.
- Fat mal-absorption including obstructive jaundice.
- Elderly age due to decreased elimination of the drugs.
- Drug potentiation (see above).

Factors decreasing the action and response of oral anticoagulants

- Nephrotic syndrome.
- Hereditary resistance.
- Recent therapeutic administration of vitamin K.
- Drug antagonism (see above).

Preparations and Doses:**A) Coumarin Derivatives**

- **Warfarin** (*Coumadin, Haemofarin, Marevan, or Marivanil*):

- Oral: Initial loading dose: 5-10 mg/day.

Maintenance dose: 2-10 mg according to prothrombin time and INR.

- I.v.: 50 mg.

- **Dicumarol (Hemofarin):** 100 mg

B) Indanedione Derivatives

- Phenindione (*Dindevan*)

- Diphenadione.

- Anisindione: - Its metabolites cause a red-orange discoloration of the urine.

- It is used mainly in patients who cannot tolerate the warfarin.

- Loading dose: 300 mg on day one, 200 mg on day two, and 100 mg on day three, then a daily maintenance dose 50-250 mg adjusted according to INR.

Fibrinolytics (Thrombolytics)

Physiological Considerations

Anti-Coagulation (Limiting Factors) inhibits extension of the thrombus by:

1- **Relaxation of the blood vessels:** as the **vessel relaxes**, blood flow returns, diluting the activated clotting factors.

2- **Removal of activated factors:** by the liver and the reticulo-endothelial system.

3- **Prostacyclin:** is secreted from the vascular endothelial cells. It is a powerful inhibitor of platelet aggregation.

4- **Circulating inhibitors** such as:

- **Anti-thrombin III (AT-III):** It regulates factors IIa (thrombin), IXa, Xa, XIa and XIIa.

- **Protein C** (vitamin K⁺ dependent protein) and its **cofactor S**: they regulate factors V and VIII.

5- **Fibrinolytic System** (figure 4-20)

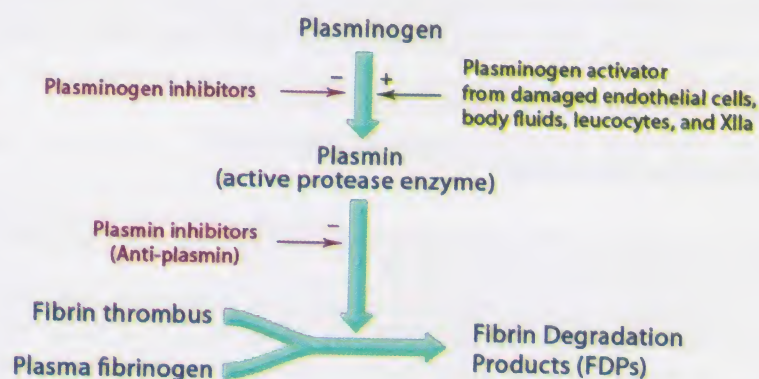


Figure 4-20: Fibrinolytic system

Fibrinolytics (Thrombolytics)

Action:

- They accelerate clot lysis because they act as **plasminogen activators** (see above).

They differ from other antithrombotic agents in that they actually dissolve established clots rather than interfering with initiation and propagation of thrombosis.

Uses:

These drugs act best when given soon after onset of symptoms before thrombi are highly cross linked and more resistant to thrombolysis.

1- **Acute arterial thrombosis** such as

- **Peripheral vascular diseases.**

- **Acute myocardial infarction.**

- **Cerebral non-hemorrhagic strokes.**

They should be given **within 3-4 hours of the symptoms.**

Recently, magnetic resonant imaging (MRI) is done to locate arterial occlusions, followed by superselective intra-arterial thrombolysis by **intra-arterial injection of the fibrinolytic therapy**. This is beneficial in patients with acute stroke who present after are 3-4 hours from the onset of symptoms.

2- **Pulmonary thrombo-embolism:** they should be given **within 48 hours** of the symptoms.

3- **Deep venous thrombosis (DVT):** they should be given **within 7 days** of the symptoms.

In both 2 and 3, oral anticoagulant therapy gives better results with lower bleeding tendency and lower cost.

4- **Dissolution of catheter thrombosis and establishment of patency of clotted indwelling venous catheters** and vascular grafts especially by urokinase 5000 units that is instilled into the occluded venous catheter without excessive pressure which could dislodge the clot or rupture the catheter. Because venous catheters may be occluded by substances other than clots (e.g., drug precipitate), urokinase is not always effective.

Agents The most commonly used clinically include:

	Streptokinase (Kibikinase, Sedonase, or Streptase)	Urokinase	Alteplase Recombinant tissue plasminogen activator (<i>Actilyse</i>)	Tenecteplase	Reteplase
Specificity	Nonspecific 1 st generation		Specific 2 nd generation		
T_{1/2} (min)	20	20	5	20	13-16
Neutralizing antibodies	Yes	No	No	No	No
Doses and uses (FDA approved)	<ul style="list-style-type: none"> • Myocardial infarction. • DVT. • Pulmonary thrombo-embolism. • Catheter thrombosis. • Peripheral arterial occlusion Doses: <ul style="list-style-type: none"> • 1.5 million units infused i.v. over 30-60 minutes. Or • 20,000 units as an intra-coronary bolus followed by 2000-4000 units/minute for 30-90 minutes. 	<ul style="list-style-type: none"> • Myocardial infarction. • Pulmonary thrombo-embolism. • Catheter thrombosis. Doses: <ul style="list-style-type: none"> • 6000 units/min infused intra-coronary for up to 2 hours. Or • 4400 units/kg infused over 10 minutes followed by 4400 units/kg/hour for 12 hours. Or • 5000 units for catheter thrombosis. 	<ul style="list-style-type: none"> • Myocardial infarction: 100 mg infusion over 90 minutes to 3 hours. • Cerebro-vascular accident: 0.9 mg/kg (maximum 90 mg) infused over 60 minutes. • Pulmonary thrombo-embolism 	<ul style="list-style-type: none"> • Myocardial infarction: single bolus 30-50 mg depending on weight in kg. 	<ul style="list-style-type: none"> • Myocardial infarction: two bolus injections 10 units each given 30 minutes apart.

Side Effects

1- **Hemorrhage:** It is the most common complication especially if other antithrombotic agents are used as heparin. It can be treated by cryoprecipitate and aminocaproic acid to inhibit plasmin activity. If heparin was received, it can be reversed by protamine sulfate.

2- Allergic reaction.

3- **Ineffectiveness** due to presence of neutralizing antibodies especially with streptokinase.

4- **Cholesterol emboli** that rarely occur resulting in **purple toe syndrome** and multi-organ failure.

5- **Allergic reactions** especially with streptokinase.

Contraindications

1- Cerebral: - Massive cerebral ischemic changes,

- Signs of intracranial hypertension on CT scan.

- Seizures at the onset of a stroke.

- Previous stroke or serious head injury within the preceding 3 months.

- Prior history of intracranial hemorrhage.

2- Bleeding: - Active or recent visceral bleeding (other than menses).

3- Cardiovascular: - Aortic dissection.

- Severe uncontrolled hypertension (> 180/110 mm Hg).

- Signs of pericarditis.
 - Cardiogenic shock (except due to massive pulmonary thrombo-embolism).
 - Traumatic or prolonged (> 10 min) cardiopulmonary resuscitation.
- 4- Traumatic: - Major surgery within the past 3 weeks.
- Major trauma.
 - Arterial or lumbar puncture in the preceding 2 weeks.
 - Recent retinal laser surgery.
- 5- Hematological: - Significant thrombocytopenia (platelet count < 100,000/ μ L).
- Concomitant use of heparin or oral anticoagulants.
- 6- Pregnancy.

Control:

- **The thrombin time** is the most sensitive test for monitoring of the status of the fibrinolytic system. If it is prolonged more than 5-7 times normal, the incidence of hemorrhage is very high.

Coagulants Therapy

They are drugs that enhance clot formation to prevent excessive bleeding e.g., during surgical procedures. They include:

- Anti-plasmins (anti-fibrinolytics or anti-thrombolytics).
- Vitamin K.
- Protamine.
- Activated factor VII (F VIIa).

Anti-Plasmins (Anti-Fibrinolytics or Anti-Thrombolytics)

They inhibit plasminogen activation and encourage clot stabilization.

1- Aprotinin (*Trasylol* or *Aprotinin*)

It is a complex polypeptide molecule belonging to the family of serine protease inhibitors. It is extracted from bovine lung.

Action:

- The exact mechanism is unknown, but complex activation-interaction of different systems may be involved:
 - Aprotinin is a naturally occurring **non-specific inhibitor of serine proteases such as plasmin, kallikrein, and trypsin**. Activation of humoral and coagulation systems may occur (such as during contact of blood during cardiopulmonary bypass tubing) where **factor XIIa** is first generated from factor XII, which then interacts with **prekallikrein and high molecular weight kininogen (HMWK)** to form kallikrein as well as promote the activation of the other coagulation factors. Once activated, **kallikrein** functions to stimulate and accelerate the generation of **bradykinin** from HMWK, factor XIIa, angiotensin, and complement activation. Factor XIIa, in turn, also interacts with **fibrinogen to produce plasmin**. Aprotinin prevent the above humoral and coagulation pathways.
- The effects of aprotinin on the coagulation cascade are dependent on the circulating plasma concentrations, expressed as **kallikrein inactivation units (KIU/mL)**. The affinity of aprotinin to plasmin and kallikrein occurs at different levels:
 - At a plasma level of 125 KIU/mL, aprotinin inhibits plasmin which in turn inhibits fibrinolysis and complement activation.
 - At a plasma level of 250-500 KIU/mL, aprotinin inhibits kallikrein which in turn:
 - reduces blood coagulation mediated via contact with anionic surfaces and in critically ill patients by reducing kinin activation.
 - inhibits neutrophils mediated via kallikrein. This prevents inappropriate platelet activation. Activation of neutrophils causes secondary activation of platelets by release of Cathepsin G from the neutrophils. Recently, it has been demonstrated that aprotinin prevents the release of Cathepsin G from the neutrophils which in turn prevents inappropriate activation of the platelets.
 - Aprotinin **preserves platelet function** by preserving the platelet surface glycoproteins (IIb/IIIa), which is necessary for platelet-fibrinogen interaction and clot formation. Therefore aprotinin reduces blood loss.
 - Aprotinin has also **anti-inflammatory actions** which is effective as that of methylprednisolone, but only achieved at high doses. This action is due to the following reasons:

- It decreases cytokines (pro-inflammatory group), which is activated by the tubing of CPB and increases anti-inflammatory cytokines such as interleukin-10.
- It has anti-kallikrin activity.
- It decreases interleukin-6 and leukocyte elastase activity.
- It decreases airway nitric oxide production.

Indications:

It is highly effective in decreasing perioperative blood loss and transfusion requirements by 40-80% especially during the usage of extracorporeal circulation.

- Repeated operation.
- Patient's refusal for blood products e.g., Jehovah's witnesses.
- High risk patients for postoperative bleeding due to recent aspirin ingestion or other antiplatelet agents.
- Patients with coagulopathy.
- Possible long and complicated procedures involving the heart and aorta.

Pharmacokinetics:

After i.v. administration, aprotinin undergoes rapid total extravascular distribution:

- Plasma half-life = approximately 2-2.5 hours.
- Terminal half-life = approximately 10 hours.

Side Effects:

- 1- **Allergic reactions up to anaphylaxis** (< 0.5%) especially on repeated exposure within 12 months; therefore, it is recommended that a test dose of 1 mL be given first when possible, before its full dose.
- 2- It artificially prolongs the celite-activated clotting time (celite-ACT) in presence of heparin, so this may cause inadequate coagulation during cardiopulmonary bypass. The kaolin-ACT is better used because it is less affected by aprotinin and it appears that the kaolin activator absorbs aprotinin from the blood.
- 3- It may increase the incidence of renal failure, myocardial infarction, heart failure, stroke, or encephalopathy due to its antifibrinolytic action. Consequently, the use of aprotinin in coronary bypass surgery has markedly decreased.

Dose:

a- High doses of Hammersmith regimen:

- A test dose: 1.4 mg (10 000 KIU) (1 mL) is given at first i.v. at least 10 minutes before the loading dose, followed by close observation for signs of an allergic reaction.
- The loading dose: 280 mg (2 million KIU) (200 mL) over 20-30 min via a central venous catheter.
- The cardiopulmonary bypass pump is also primed with additional 280 mg (2 million KIU) added to the priming solution.
- The maintenance dose: 70 mg/h (500 000 KIU/h) infusion for the duration of surgery.

b- Low dose is also effective. It equals 1/2 and 1/4 of the Hammersmith regimen. It is less expensive.

2- Tranexamic Acid (*Amstat, Cyclokapron, or Kapron*)

Action: It is less effective, and used instead of aprotinin.

Dose: 5-10 mg/kg i.v. then 1 mg/kg/h.

Advantages:

- Less allergic reactions.
- It does not affect activated clotting time (ACT).

However, it is less effective.

3- Epsilon Amino-Caproic Acid (*EACA*).

Action: It acts as lysine analogs and attaches to the lysine-binding sites of plasmin and plasminogen preventing their activity and inhibiting plasminogen activation, resulting in inhibition of primary fibrinolysis, which is due to excessive plasminogen activators e.g. urokinase or tissue type plasminogen activator.

Dose: 15 mg/kg/h i.v. infusion until bleeding is controlled (maximum 24 g in 24 hours), followed by 6 g/6 h i.v. or oral for 7-10 days (for hereditary deficiency of a coagulation factor).

Protamine Sulfate (*Protam*)**Action:**

- It is a highly positively charged protein (a strong organic base polycation) that binds and effectively inactivates the long polysaccharide chains of the unfractionated heparin (a highly negatively charged polysaccharide) (a strong organic acid polyanion). Heparin-protamine complexes are formed without

anticoagulant activity i.e., heparin can not bind anti-thrombin III, which then is removed by the reticulo-endothelial system.

- Protamine is **much less effective** for reversing the effect of LMWH than UFH.
- Protamine has no reversal effect on fondaparinux.

Control:

- By repeating ACT **3-5 min after reversal** during cardiopulmonary bypass as additional increments of protamine may be needed.
- Because heparin rebound is possible, **ACT is repeated 20 min later**. It is optimal to give protamine at 2 times after cardiopulmonary bypass (once after the bypass and again 1-2 hours later) to prevent heparin rebound. After initial reverse of heparin by protamine, the heparin which is sequestered in tissues is released slowly into the circulation where it can perform its anticoagulant function again.

Dose: is calculated by one of the following methods:

A) For UFH:

1- Based on the heparin dose:

- **1-1.3 mg protamine for each 100 units (1 mg) of heparin.**
- Only the initial dose of heparin is counted. The subsequently added doses of heparin required to keep the ACT level > 480 sec are not considered due to heparin metabolism and elimination.

2- Based on heparin-dose-response curve: see "chapter of cardiac surgery".

3- Based on automated heparin-protamine titration assays.

Pre-measured amounts of protamine are added in varying quantities to several tubes each containing a blood sample. The tube which **protamine concentration best matches** the heparin concentration, **will clot first**, but clotting is delayed in tubes containing either too much protamine (as excess protamine has an anticoagulant action) or too little protamine (as it is not enough to reverse heparin).

Therefore, **the protamine dose =**

Concentration of protamine in the tube that clots first X patient's calculated blood volume.

but if serious bleeding occurs, protamine sulfate 1 mg per 100 anti-factor Xa units of LMWH is given (1 mg of enoxaparin = 100 anti-factor Xa units).

B) For LMWH: Although it is less effective, but if serious bleeding occurs, protamine sulfate 1 mg per 100 anti-factor Xa units of LMWH is given (1 mg of enoxaparin = 100 anti-factor Xa units) is given.

Side Effects:

1- Excess protamine (in a dose double than that used clinically) has **an anticoagulant action** because

- Transient thrombocytopenia occurs.
- Protamine binds to thrombin, inhibiting thrombin's ability to convert fibrinogen to fibrin.

2- Hypotension may occur due to:

- **Acute systemic vasodilatation due to histamine release** on rapid injection of protamine (i.e., pharmacologic action).
- **Anaphylactic** (IgE mediated) **or anaphylactoid reaction** (immune or non-immune idiosyncratic reactions).

N.B.: Protamine-containing insulin used in treatment of diabetes mellitus can increase allergic reactions (due to developing antibodies against protamine).

- **Marked pulmonary vasoconstriction** which causes pulmonary hypertension and leads to right ventricular failure.

- **Non-cardiogenic pulmonary edema** due to a delayed anaphylactoid reaction, as there are increased plasma levels of C_{5a} anaphylatoxins and thromboxane which cause pulmonary vasoconstriction and bronchospasm.

Treatment of Protamine Hypotension:

a- Cases with low pulmonary artery pressure: (due to systemic vasodilatation and anaphylaxis):

- Rapid volume infusion.
- Vasopressors e.g., phenylephrine.

b- Cases with high pulmonary artery pressure: (due to delayed anaphylactoid reaction):

- Inotropes e.g., isoprenaline, amrinone, or epinephrine (0.1 mg increments).
- If severe hypotension is present, re-heparinization is done again and the patient is returned back to the cardiopulmonary bypass to maintain the circulation.

N.B.: Slow infusion of diluted protamine solution is the best prophylaxis.

- Recently, Yang developed a **reactor device** containing **immobilized protamine** (called a **protamine bioreactor**) that can be placed on the distal end of the extracorporeal circuit. The protamine bioreactor

binds and selectively removes heparin in the extracorporeal device before it is returned to the patient. The device successfully prevents protamine-induced complications in dogs. It is a hope that in the near future, the device can be used clinically to remove heparin without administration of protamine to the patients, so as to avoid its side effects.

Recombinant Activated Factor VII (rF VIIa) (Novoseven)

Mechanism:

- 1- It acts directly at the site of bleeding by **binding to locally expressed tissue factor** (at the site of vascular injury). The complex that forms activates factor X of the common coagulation pathway and factor IX of the intrinsic coagulation pathway and allows a fibrin clot to develop.
- 2- It enhances platelet function.

Uses:

It is used to restore hemostasis in severe intractable bleeding that does not respond to standard measures.

- 1- Hemophilia A.
- 2- Major trauma, orthopedic and cardiac surgeries.

Doses:

4500 IU/kg over 2-5 minutes followed by 3000-6000 IU/kg depending on the severity of bleeding.

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Sources of the Hematological Drugs

- **Aspirin** is derived from a plant origin.
- **Eptifibatide** (*Integrilin*): is a synthetic heptapeptide similar to that found in snake venom from *Sistrurus barbouri*.
- **Abciximab** (*Reopro*): is a recombinant humanized monoclonal antibody derived from bacteria.
- **UFH**: is derived from porcine intestine or bovine lung.
- **LMWH**: is derived from the heparin.
- **Heparinoids**: are derived from porcine intestinal mucosa.
- **R-Hirudin**: is isolated from the **salivary glands of the medicinal leech**.
- **Streptokinase**: is a bacterial protein.
- **Ancrod** is an enzyme derived from the Malayan pit viper.
- **Protamine**: is derived from the sperms of salmon fish.
- **Aprotinin**: is derived from bovine lung.

Drugs Acting on the Wall of Blood Vessels and Capillaries

These drugs are not hematological drugs as they have no antifibrinolytic actions and have no effect on coagulation factors, but they are used to decrease blood loss by improving the function of the vessel walls.

- 1- **Ethamsylate** (*Dicynone, Eselinate, Hemostatine, Haemostop, or Hemostat*):
It acts selectively on the capillary wall, rapidly normalizes its resistance and permeability.
- 2- **Diosmin** (*Daflon, Dafrex, Diosed, Dioven, Insuven*).
- 3- **Rutin** (*Ruta-C, Rutalex, or Rutin C* with vitamin C) as vitamin C improves rutin action.
- 4- **Calcium dobesilate** (*Doxium or Dilasal*).

DRUGS ACTING ON THE CENTRAL NERVOUS SYSTEM

In the previous chapter "Pharmacology of anesthesia and intensive care" many drugs acting on the central nervous system are discussed.

Antiepileptic Drugs (Anticonvulsant Drugs)

General Principles of the Drug Therapy

- 1- Proper choice of the type of the seizure is essential for the choice of drugs.
- 2- Starting with a single drug is preferred because combination therapy enhances toxicity and drug interactions may occur between antiepileptic drugs. If monotherapy fails, substitution with another drug or addition of a second drug is necessary.
- 3- As these drugs have a narrow safety margin (narrow therapeutic index), the dose should be adjusted according to:
 - the plasma level (if available)
 - patient's response and tolerance.
- 4- Effective therapy must never be stopped suddenly, otherwise status epilepticus may occur. The dose of the drugs should be reduced gradually.
- 5- Full drug therapy should continue for 2-3 years after the last fit. After that, drugs are withdrawn slowly over a period of at least 6 months. If another fit occurs, a further 2-3 years period is necessary before another trial of drug withdrawal is attempted.
- 6- During pregnancy, carbamazepine is used in the smallest possible dose because it has no teratogenic effect.
- 7- All these drugs act by enhancement of GABA transmission.

Individual Drugs

	Carbamazepine (Tegretol, Carbatol, Mazemal, or Tonoclon)	Oxazolidinediones	Valproic acid or Na⁺ valproate (Depakine, Convulex, or Valpokin)	Ethosuximide (Zarontin)
Chemistry	It is related to tricyclic antidepressants.	Agents: Trimethadione, Para-methadione, Dimethadione.	It is a derivative of carboxylic acid.	It belongs to succinimide group. Other agents include: phensuximide, and methsuximide.
Action	1- Antiepileptic action: - Voltage- dependent block of sodium channels. - It inhibits the uptake and release of noradrenaline from brain synapses. 2- It sensitizes renal tubules to the action of antidiuretic hormone.	1- Antiepileptic action.	1- Antiepileptic action: by • Voltage- dependent block of sodium channels. • Increased Ca ⁺⁺ -dependent K ⁺ conductance. • Inhibition of GABA transaminase.	1- Antiepileptic action. • Reduction of slow Ca ⁺⁺ conductance in thalamic neurons.
Uses	1- Antiepileptic action: • Partial seizures. • Generalized tonic-clonic seizures (grand mal epilepsy). 2- Central or nephrogenic diabetes insipidus. 3- Trigeminal neuralgia (1st choice).	1- Antiepileptic action: • Petit mal (1 st choice).	1- Antiepileptic action: • All seizure types, especially idiopathic generalized epilepsy.	1- Antiepileptic action • Un-complicated absence seizures. • Refractory cases only due to side effects.
Pharmacokinetics	• It is well absorbed orally. • Plasma protein binding 75%. • T _{1/2} 8-24 hours. • Therapeutic level = 4-10 µg/mL which is higher than phenytoin and phenobarbitone.	• It is well absorbed orally. • Plasma protein binding is very minimal. • T _{1/2} 30-60 hours. • Therapeutic level = 40-100 µg/mL.	• It is well absorbed orally. • Plasma protein binding is 90%. • T _{1/2} 7-17 hours. • Therapeutic level 40-100 µg/mL. • Metabolism: in the liver by conjugation with	• It is not protein-bound. • T _{1/2} 20-60 hours • Metabolism: in the liver (75%).

	<ul style="list-style-type: none"> Metabolism: in the liver to active metabolites. 	<ul style="list-style-type: none"> Metabolism: in the liver to inactive metabolites. 	glucuronic acid leading to active metabolites	
Side effects	All side effects are dose dependent: 1- Gastrointestinal upset: anorexia, nausea, vomiting, and epigastric pain. 2- Allergic reactions: rash, fever, or systemic lupus erythematosus (with phenytoin), photosensitivity (with carbamazepine), and exfoliative dermatitis (ethosuximide). 3- Liver dysfunction: liver function tests should be done regularly. 4- Neurological: nystagmus, ataxia, diplopia, vertigo, behavioral changes, and peripheral neuritis.			
	5- Hematological: <ul style="list-style-type: none"> Aplastic anemia and pancytopenia. Agranulocytosis. 6- Endocrinal: <ul style="list-style-type: none"> Water toxicity and Hyponatremia due to antidiuretic hormone like action. 		5- Hair loss (thinning and curling). 6- Weight gain and increased appetite. 7- Teratogenic: especially spina bifida. 8- Interference with ketone tests because it is partially eliminated in the urine as keto-metabolites.	5- Hematological Dyscrasias. 6- Renal: nephrosis. 7- Myasthenia.
Doses	1- Oral: <ul style="list-style-type: none"> Adult: 200 mg/12 hours, increased gradually to 600-1200 mg/day. Child: 20-30 mg/kg/day; maximum dose is 1 gm/day. 	1- Oral: 20-40 mg/kg/12-24 hours.	1- Oral: 15-30 mg/kg/12 hours.	1- Oral: <ul style="list-style-type: none"> Adult: 900-1200 mg/day. Child: 20-60 mg/kg/day.
Drug interactions	<ul style="list-style-type: none"> It is a potent enzyme inducer, increasing metabolism of phenytoin, primidone, valproic acid, oral contraceptive pills, and clonazepam. Cimetidine and erythromycin inhibit its metabolism 	<ul style="list-style-type: none"> Its metabolism is inhibited by valproic acid. 	<ul style="list-style-type: none"> Valproic acid inhibits metabolism of phenobarbitone, phenytoin, carbamazepine, and succinimides i.e., an enzyme inhibitor. 	

Phenytoin (*Epanutin, Ipanten, or Phenytoin*): is discussed above in antiarrhythmic drugs.

Barbiturates: such as

1- Phenobarbitone (*Comidal-L* with phenytoin)

- It is one of the barbiturates.
- It has a long half-life of 70-140 hours.
- It is metabolized mainly in the liver (75%) and excreted by the kidneys (25%).
- It is an enzyme inducer
- Side effects: sedation, mood depression, cognition and memory impairment. Hyperactivity and aggression in children
- Doses: 60-180 mg orally at night.

2- Primidone:

It is a prodrug and is metabolized to phenobarbitone. It is less tolerated than phenobarbitone.

3- Thiopentone: is discussed before.

Benzodiazepines: such as

1- Clonazepam (*Amotril, Apetryl, Clonopin or Rivotril*):

- It is a benzodiazepine.
 - Plasma protein binding is 90%
 - $T_{1/2}$ 30-40 hours.
 - Metabolism in the liver
 - Side effects: sedation and emotional instability.
 - Dose: Oral: 4-8 mg/day in divided doses.
- I.v. route is used in management of status epilepticus.

2- Diazepam: is discussed before.

Magnesium Sulphate is discussed above.

New Antiepileptic Drugs:

	Vigabatrine (Sabril)	Lamotrigine (Lamictal, Lamotrine, or Larogen)	Gabapentin (Conventin, Gaptin, or Neurontin)	Topiramate (Topamax, or Topiramate)	Tiagabine
Pharmacokinetics	<ul style="list-style-type: none"> • Duration: is prolonged because it produces permanent inhibition of GABA transaminase enzyme increasing GABA action, so its action is prolonged for several days until the enzyme regenerates. • It is not protein bound. • It is excreted mainly by the kidneys. 	<ul style="list-style-type: none"> • It is metabolized mainly in the liver. 	<ul style="list-style-type: none"> • It is excreted unchanged by the kidneys. • $T_{1/2}$ 5-7 hours. 	<ul style="list-style-type: none"> • It is metabolized in the liver. 	<ul style="list-style-type: none"> • It is metabolized mainly in the liver.
Side effects	<ul style="list-style-type: none"> • Mainly neurological as sedation, dizziness, ataxia, somnolence, depression and psychosis. • Peripheral edema. 	<ul style="list-style-type: none"> • Mainly neurological as headache, diplopia, sedation, ataxia, and tremors. • Stevens-Johnson syndrome. 	As lamotrigine.	<ul style="list-style-type: none"> • Neurological symptoms as cognitive dysfunction, paresthesia, anorexia and weight loss. • Nephro-lithiasis due to inhibition of carbonic anhydrase enzyme. • It is the only new antiepileptic which has teratogenic effects. 	<ul style="list-style-type: none"> • Neurological symptoms as dizziness. • Gastro-intestinal upset.
Dose	Oral: 2-3 gm/ day. (the first of the new drugs)	Oral: 150-200 mg/ day	Oral: 1.2 gm/ day in 3 divided doses.	Oral: 100-400 mg/ day in 2 divided doses.	Oral: 15-30 mg/ day in 3 divided doses

N.B.: **Gabapentin** (structurally similar to γ -aminobutyric acid "GABA") and **pregabalin** (structurally similar to gabapentin) act by activation of α_2 -delta subunit of voltage dependant calcium channel and peripheral sodium channels suppressing the spontaneous neuronal firing of the traumatized nerves. Despite their name, and similarities (a structural analog of gamma-amino butyric acid "GABA"), they do not bind to GABA receptors.

N.B.: Anticonvulsant Drugs are used in chronic Pain Management:

- Patients with neuropathic pain especially trigeminal neuralgia, postherpetic neuralgia, HIV neuropathy, diabetic neuropathy and pain of spinal cord injury.
- As an effective adjuvant for postoperative pain especially gabapentin.

Antidepressant Drugs

They include:

- 1- Selective serotonin reuptake inhibitors (SSRIs).
- 2- Tricyclic antidepressants.
- 3- Monoamine oxidase inhibitors (MAOIs).
- 4- Atypical antidepressants.

Depression is also treated by psychotherapy and electroconvulsive therapy (ECT).

1- Selective Serotonin Reuptake Inhibitors (SSRIs):

Actions:

They block reuptake of serotonin at presynaptic membranes with relatively little effect on adrenergic, cholinergic, histaminergic, or other neuro-chemical systems; therefore, they have few side effects.

Agents: SSRIs are the most common used antidepressant drugs. They include:

- Citalopram (Celexa).
- Escitalopram.
- Fluoxetine (Prozac).
- Nefazodone (Serzone).
- Paroxetine (Paxil).
- Sertraline (Zoloft).
- Trazodone (Desyrel).
- Fluvoxamine (Luvox).

Indications:

They are used in treatment of:

- Depression.
- Panic disorders.
- Posttraumatic stress disorder.
- Bulimia.
- Dysthymia.
- Obsessive-compulsive disorder.
- Irritable bowel syndrome.

Side Effects:

- 1- Insomnia, agitation, and headache.
- 2- Nausea and vomiting.
- 3- Sexual dysfunction.
- 4- Abrupt withdrawal of SSRIs can lead to a **discontinuation syndrome** (after 1-3 days) that can mimic serious illness and can be distressing and uncomfortable. It may cause dizziness, irritability, mood swings, headache, nausea and vomiting, dystonia, tremor, lethargy, myalgia, and fatigue.
- 5- Fluoxetine therapy can lead to:

- Appetite suppression.
- Hepatic cytochrome P-450 enzyme inhibition with increase plasma levels of tricyclic antidepressants, antiarrhythmic drugs, and some β -blockers resulting in increased their actions.

6- **Serotonin syndrome**: it is associated with the usual dose or overdose of some drugs or due to drug interaction between serotonergic drugs. The clinical picture ranges from mild to severe life-threatening effects such as agitation, delirium, altered mental status, autonomic hyperactivity, hyperreflexia, clonus, and hyperthermia.

Treatment is supportive and symptomatic measures. Cyproheptadine, a 5-HT_{2A} antagonist, can be used to bind serotonin receptors.

N.B.: Drugs associated with serotonin syndrome (in the usual or over-dosage):

- | | |
|---|---|
| • SSRIs. | • Atypical and cyclic antidepressants. |
| • MAOIs. | • Anticonvulsant drugs (valproate). |
| • Antimigraine drugs (sumatriptan). | • Bariatric drugs (sibutramine). |
| • Antibiotics (linezolid, ritonavir). | • Antitussive drugs (dextromethorphan). |
| • Drug of abuse (ecstasy, LSD). | • Dietary supplements (St. John's wort, ginseng). |
| • Analgesics (meperidine, fentanyl, tramadol, pentazocine). | |
| • Antiemetics (ondansetron, granisetron, metoclopramide). | |
| • Lithium. | |

Drug interactions associated with severe serotonin syndrome:

- Phenylzine and meperidine.
- Tranylcypromine and Imipramine.
- Phenylzine and SSRIs.
- Paroxetine and buspirone.
- Linezolid and Citalopram.
- Modobemide and SSRIs.
- Tramadol, venlafaxine, and mirtazapine.

2- Tricyclic Antidepressants:**Action:**

- They have **analgesic action (at low doses)** and **anti-depressant action (at the usual doses)** by **blockade of presynaptic reuptake** of the amine neurotransmitters "norepinephrine, serotonin, or both". Therefore, the concentration and duration of action of these substances at the synapse in brain stem and spinal cord are increased and thereby enhancing activity in the descending inhibitory pain pathway. The **analgesic action** appears **after 3-4 days** of treatment, while the **antidepressant action** appears **after 3-4 weeks**.
- They also **block sodium and calcium channels** and suppress ectopic neuroma discharge.
- They have **opioidergic effect**.
- They also **inhibit uptake of adenosine** at adenosine receptors.
- They also normalize sleep pattern, and decrease anxiety and depression.

Agents:

- Amitriptyline (*Elavil*): is the most common used and in a starting dose 10-25 mg.
- Clomipramine (*Anaframil*).
- Doxepin (*Sinequan*).
- Nortriptyline (*Pamelor*).
- Venlafaxine (*Effexor*).
- Desipramine (*Norpramin*).
- Imipramine (*Tofranil*).
- Protriptyline (*Vivactil*).
- Bupropion (*Wellbutrin*).

They are more effective as analgesic.

Uses:

- They are the old generation and used in depression in only selected cases.
- Patients with neuropathic pain e.g., post-herpetic neuralgia and diabetic neuropathy.

Pharmacokinetics:

They have extensive first-pass hepatic metabolism.

Half lives are between 1-4 days.

Side Effects:

- 1- **Antimuscarinic (anticholinergic) effects:** dry mouth (xerostomia), impaired visual accommodation and mydriasis, tachycardia, flushed dry skin, urinary retention, and constipation especially **amitriptyline** and **doxepin**. Central symptoms are also present such as delirium and seizures.
- 2- **Antihistaminic effects** (H_1 and H_2): sedation and increased gastric pH especially **amitriptyline**, **doxepin**, **clomipramine**, and **trazodone**.
- 3- **α -adrenergic blockade:** orthostatic hypotension especially **imipramine**.
- 4- **Quinidine-like effect:** especially **amitriptyline**.
- 5- **Drug interaction with anesthetics** is discussed in chapter "The practice conduct of Anesthesia".

Overdose:

Potentially lethal doses of these drugs may only be 5-10 times the daily therapeutic doses. The clinical picture includes severe central antimuscarinic (anticholinergic) effects (as above) with ventricular arrhythmias and myocardial depression then death. Fatal conditions are predicted when QRS duration in limb leads is more than 100 milliseconds. Activated charcoal and supportive treatment are needed.

3- Monoamine Oxidase Inhibitors (MAOIs):

They are discussed in chapter "The Practice Conduct of Anesthesia".

4- Atypical Antidepressants:**Actions:**

They produce other actions including inhibition of reuptake of serotonin and dopamine, antagonism of specific serotonin receptors, dopamine receptor blockade, and presynaptic α_2 -blockade resulting in increases in norepinephrine and serotonin release, and histamine receptor blockade.

Agents:

- Bupropion (*Wellbutrin*).
- Trazodone (*Desyrel*).
- Nefazodone (*Serzone*).

CHEMOTHERAPY

It includes:

a- Antimicrobials:

• They are used in treatment of infection. They include antibacterial, antifungal, and antiviral drugs. They are either:

- **Antibiotics:** that are derived from living organisms.

- **Chemotherapeutic agents:** that are synthetic drugs.

• They are used to kill microorganisms (i.e., **bactericidal**) or stop growth and multiplication of microorganisms (i.e., **bacteriostatic**).

b- **Antiparasitic agents:** they include anti-helminthics and anti-protozoal drugs.

c- **Anticancer chemotherapy (cytotoxic drugs):** they are used in treatment of neoplastic diseases.

Both antiparasitic and anticancer drugs are out of the concept of this book.

ANTIMICROBIALS

Classification of Antibacterial Chemotherapy

A) According to Their Effect on the Bacteria:

They are either:

• **Bactericidal:** i.e., kill the microorganism and eradicate the infection with no need for the body defense mechanisms e.g. penicillins and aminoglycosides.

• **Bacteriostatic:** i.e., they stop the growth of microorganisms with the need for the body defense mechanisms to eradicate the infection e.g., tetracyclines and chloramphenicol.

N.B.: A bactericidal drug should not be combined with a bacteriostatic one for a highly sensitive organism (the bacteriostatic drug will inhibit the growth of the bacteria abolishing the action of the bactericidal one which acts only on rapidly growing or dividing organisms).

B) According to the Antibacterial Spectrum:

• **Broad Spectrum Antimicrobials:** they involve all spectra (both gram positive and gram negative) except resistant negative bacilli, but some antibiotics can affect the resistant negative bacilli. For example:

1- Tetracyclines: are the broadest spectrum antimicrobials. They are more effective on positive cocci. They are also effective against rickettsia, brucella, vibrio cholera, trachoma, coryne bacterium acne, and Entameba histolytica.

2- Chloramphenicol: is more effective on negative bacilli including salmonella.

Both 1 and 2 are bacteriostatic.

3 - Broad spectrum penicillins such as ampicillin: are more effective on negative bacilli including salmonella.

4- Cephalosporins: also affect anerobic bacteria.

5- Quinolones: are more effective on negative bacilli including salmonella.

6- Co-trimoxazole: is more effective on positive cocci including salmonella.

7- Rifampin: is also effective against tuberculosis.

From 3 up to 7 are bactericidal.

• **Narrow Spectrum Antimicrobials:**

a- **Drugs Effective Against Gram Positive Organisms** (as positive and negative cocci and positive bacilli):

1- Penicillin G, and penicillinase resistant penicillins.

2- Erythromycin.

3- Clindamycin.

4- Vancomycin.

5- Bacitracin.

b- **Drugs Effective Against Gram Negative Organisms** (as non-resistant negative bacilli, and tuberculosis):

1- Aminoglycosides.

2- Polymixin.

c- **Drugs Effective Against Cocci (Positive and Negative) and Nonresistant Negative Bacilli:**

- Sulphonamides.

The Most Common Spectrum

Spectrum	Diseases (Uses)
Positive cocci <ul style="list-style-type: none"> • Staphylococci • Streptococci • Pneumococci 	<ul style="list-style-type: none"> - Skin infection, otitis media, osteomyelitis, and upper respiratory tract infection. - Tonsillitis, rheumatic fever, and infective endocarditis. - Pneumonia.
Negative cocci <ul style="list-style-type: none"> • Meningococci • Gonococci 	<ul style="list-style-type: none"> - Cerebrospinal meningitis. - Gonorrhea.
Positive bacilli <ul style="list-style-type: none"> • Diphtheria and clostridia • Spirochetes as Treponema Pallidum 	<ul style="list-style-type: none"> - They release exotoxins; therefore, they are treated mainly by antitoxins. - Syphilis.
Negative bacilli <ul style="list-style-type: none"> • Hemophilus influenza • Shigella and Shigella-like • E. coli • Proteus • Pseudomonas • Resistant negative bacilli • Salmonella • Mycobacteria tuberculosis 	<ul style="list-style-type: none"> - Severe complicated influenza. - Shigellosis and bacillary dysentery. - Urinary tract infection. - Urinary tract infection. - Typhoid fever. - Tuberculosis.

C) According to the Mechanism of Action:

1) Drugs Inhibiting Bacterial Cell Wall Synthesis:

These drugs require actively proliferating microorganisms, thus they have little or no effect on non-growing bacteria and should not be given with bacteriostatic drugs. They have no effect on organisms devoid of cell wall e.g., Mycoplasma.

• β -lactam antibiotics as penicillins and cephalosporins

- inhibit enzymes responsible for synthesis of muco-polysaccharide layer of the bacterial cell membrane (acting only on the 4th phase of the cell walls) through binding to penicillin binding proteins.

and - stimulate autolytic enzymes (autolysins) resulting in lysis of the cell membrane and increasing influx of hyper-osmotic particles.

This causes entry of the water into the cells, which become swollen and rupture i.e., **bactericidal**. They do not affect the human cells because their cell walls lack the 4th phase.

• **Bacitracin, vancomycin, and cycloserine** act on the 2nd phase of cell wall and are toxic to human cells because they contain the 2nd phase also. They inhibit dephosphorylation in phospholipid carrier which transfers mucopeptide to the growing cell wall.

2) Drugs Inhibiting Protein Synthesis:

• **Tetracyclines** bind to 30 S ribosomal bacterial subunits leading to inhibition of early stage of protein synthesis which is responsible for growth and multiplication i.e., **bacteriostatic**. They also affect human ribosomes leading to **catabolic** effects.

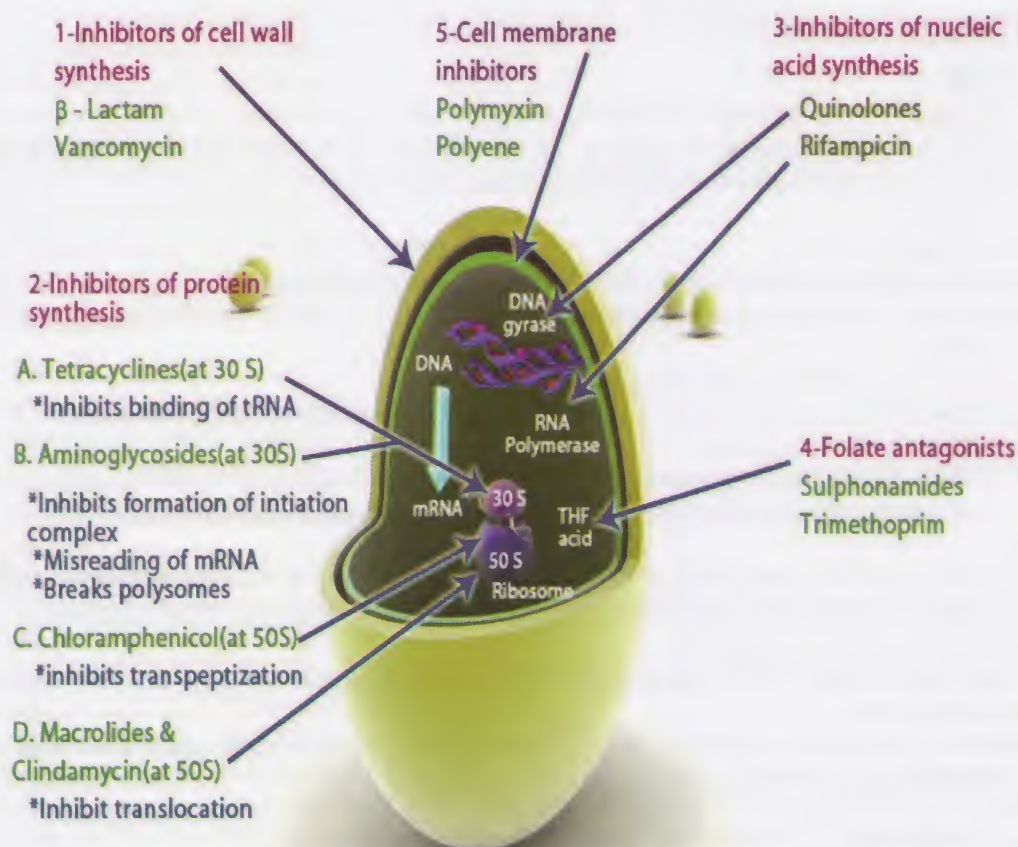
• **Chloramphenicol and macrolides as erythromycin and clindamycin** bind to 50 S ribosomal bacterial subunits leading to inhibition of late stage of protein synthesis; therefore, they are **bacteriostatic and catabolic**.

• **Aminoglycosides** irreversibly bind to 30 S ribosomal bacterial subunits leading to:

- Misreading of the genetic code which results in a change in the amino acid sequence. This produces malformed proteins; therefore, they are **bactericidal**.
- Breaking down of polysomes to nonfunctional monosomes.
- Inhibiting formation of the initiation complex.

3) Drugs Inhibiting Nucleic Acid Synthesis (Acting on DNA and RNA):

- Rifampicin inhibits DNA dependent RNA polymerase resulting in decreasing RNA synthesis.
- Rifampicin, metronidazole, nitrofurantoin, quinolones, antiviral drugs and some cytotoxic drugs act on nucleic acid metabolism by inhibiting DNA synthesis. Quinolones inhibit DNA gyrase and supercoiling. This results in unwinding of double-stranded DNA leading to inhibition of DNA replication. Rifampicin inhibits DNA-dependent RNA polymerase resulting in inhibition of RNA synthesis (figure 4-21).



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Figure 4-21: Mechanism of action of antimicrobials

4) Drugs Inhibiting Metabolic Pathways (Acting as Anti-Metabolites):

- Sulphonamides compete with PABA, due to structural similarity, for the enzyme folic acid synthetase leading to inhibition of folic acid synthesis which is a cofactor for nucleoproteins i.e., **bacteriostatic**.

They inhibit the following reaction; $\text{PABA} \xrightarrow{\text{Folic acid synthetase}} \text{Folic acid}$

- Trimethoprim competes with folic acid for the enzyme folic acid reductase resulting in inhibition of folic acid which is the active form of folic acid; therefore, it is a **bacteriostatic**.

They inhibit the following reaction; $\text{Folic acid} \xrightarrow{\text{Folic acid reductase}} \text{Folinic acid}$.

Folinic acid is essential in DNA synthesis.

- Cotrimoxazole is a combination between sulphonamides and Trimethoprim; therefore, the two bacteriostatic drugs are changed to a **bactericidal** drug

5) Drugs Affecting Cell Membrane (Cytoplasmic) Membrane Permeability:

- Antifungal drugs (nystatin and amphotericin), polymyxins, and polyenes are lipophilic drugs causing lysis of lipoprotein layer of the cell membrane. They are toxic to human leading to renal toxicity.

Inhibitors of Bacterial Cell Wall Synthesis

They include • β -lactam antibiotics which contain a β -lactam ring such as:

- Penicillins,
- Cephalosporins and cephamycins,
- Carbapenems,
- Monobactams as aztreonam,
- β -lactamase inhibitors as clavulanic and sulbactam.
- Others as vancomycin and bacitracin.

Beta Lactam Antibiotics

Penicillins

Chemical Structure:

They contain amino-penicillanic acid nucleus which contains β -lactam ring and thiazolidine ring. Penicillins differ in their R groups attached to the β -lactam ring.

Mechanism of Action:

- They are bactericidal as above.
- β -lactamase is an enzyme produced by some bacteria such as *Staphylococci*, leading to inactivation of β -lactam antibiotics and resulting in resistance to these drugs.

Spectrum: As above.

Pharmacokinetics: They are lipophobic drugs.

Absorption: - Most of them are poorly absorbed orally and destroyed by HCl of the stomach.

Distribution: - They cross the placenta

- They do not cross the normal blood brain barrier, but can cross the inflamed barriers;
- Therefore, they can be used in meningitis in large doses.

Elimination:

- They are **mainly excreted by the kidney** (20% by filtration and 80% by tubular secretion). **Probenecid** inhibits renal tubular secretion by competing with the penicillins for acid secretory mechanism resulting in prolongation of the action of penicillin.

- They are not metabolized by the liver except in patients with penicillinase enzyme (β -lactamase) producing penicilloic acid.

N.B.: Amoxicillin is better than ampicillin as it is almost completely absorbed orally with higher plasma level and produce less gastrointestinal disturbances and diarrhea.

Uses:

1- Streptococcal infections:

- Acute throat infections (as acute follicular tonsillitis).
- Wound sepsis.
- Puerperal fever.
- Bacterial endocarditis: Penicillin is given as an i.v. bolus followed by i.v. aminoglycosides, separated by a time interval. Penicillin facilitates penetration of aminoglycosides by interfering with bacterial cell wall synthesis i.e., synergetic bactericidal effect. They are used for treatment and prophylaxis.

2- Staphylococcal infections:

- Skin infection.
- Osteomyelitis.
- Otitis media.
- Upper respiratory tract infection.

3- Pneumococcal infections: pneumonia.

4- Syphilis and gonorrhea (procaine penicillin as an alternative to fluorinated quinolones).

5- Meningococcal meningitis (penicillin G or ampicillin with chloramphenicol).

6- Typhoid and paratyphoid fever (ampicillin and amoxicillin).

7- Diphtheria, tetanus and gas gangrene (penicillin and specific antitoxins).

8- Prophylaxis against recurrent rheumatic fever (benzathine penicillin 1.2 million units/month).

Adverse Effects:

They are one of the safest antibiotics used and can be used during pregnancy as they are not teratogenic.

1- Hypersensitivity reactions:

- They are the most serious side effects and may be fatal. Penicilloic acid acts as a hapten producing antigen antibody reaction with clinical pictures ranging from mild skin rash up to angioneurotic edema, bronchial asthma, and anaphylactic shock.

- They are more common with penicillin G; therefore, its use is restricted.
- There is cross-allergy among β -lactam antibiotics.
- Precautions: - They are absolutely contraindicated if there is a previous history of allergy with them.
 - Skin sensitivity test should be done before their parenteral injections.
 - Drugs for resuscitation should be available before injection such as epinephrine, corticosteroids, and antihistaminics.

2- **Resistance:** due to bacteria producing penicillinase enzyme especially staph aureus.

3- Irritation:

- Gastrointestinal upset as nausea, vomiting, and diarrhea (due to disruption of normal balance of intestinal flora) with oral routes especially agents that are incompletely absorbed orally e.g., ampicillin.

- Painful on injection via i.m. route.

- Thrombophlebitis with i.v. route.

4- **Convulsions** especially with increased blood level or intrathecal injection.

5- Adverse reactions due to salts:

- Hyperkalemia with potassium salts (penicillins are prepared as K^+ or Na^+ salts).
- Hypertension with sodium salts

6- **Ampicillin** produces - Hemolytic anemia.

- Skin rash due to lymphatic leukemia, infective mononucleosis, and renal failure.

7- **Penicillinase resistant penicillins** produce: - Agranulocytosis.

- Nephropathy.

- Hematuria.

8- During management of syphilis by penicillins:

- Masking of syphilitic manifestation may occur.

- Jarisch's - Herx - Heimmer reaction: severe syphilitic manifestations develop in patients treated with massive therapy due to killing of many spirochetes and releasing of their toxins.

Preparations:

I) Natural Penicillins:

They have a **narrow spectrum** (gram positive cocci, bacilli, and gram negative cocci) and are inactivated by β -lactamase.

- **Benzyl penicillin (penicillin G):** rapid onset, short duration, 300 000 IU/4-6 hours, only given by i.m. and i.v. routes as it is less stable with gastric acid.

- **Benzathine penicillin:** 1200 000 IU/2-4 weeks i.m.

- **Procaine penicillin:** 600 000 IU/12-24 hours i.m.

- **Fortified procaine penicillin** (0.3 mega unit procaine penicillin and 0.1 mega unit benzyl penicillin).

Both benzathine and procaine penicillins are insoluble salts of penicillin G; therefore, they have slow absorption and long duration of action.

- **Penicillin V:** is acid stable and can be given orally.

II) Semi-Synthetic Penicillins:

a) **Oral Preparations:** 250-500 mg/6 hours

- Phenoxyethyl penicillin (*Ospen*).

- Phenoxyethyl penicillin.

- Phenoxypropyl penicillin.

b) **Broad Spectrum Preparations:**

1- **Ampicillin** (*Ampicillin*, or *Epicocillin*):

Its spectrum is like the natural penicillin in addition to some gram negative bacilli, and is inactivated by β -lactamase. It is used in treatment of typhoid fever, urinary tract infection and in biliary tract infection as it is concentrated in bile.

It is taken orally (as it is stable with gastric acidity and partially absorbed through the gut leading to diarrhea) and parenterally.

2- **Amoxicillin** (*Amoxicillin*, *Alemox*, *Amoxil*, *Amoxicid*, *Biomox*, *E-Mox*, *Farconcil*, *Hiconcil*, *Ibiamox*, *Ospamox*, or *Moxipen*):

It is similar to ampicillin but completely absorbed via the gut so diarrhea does not occur.

3- **Carbenicillin and ticarcillin** (more potent)

They have a broad spectrum including *Pseudomonas* and many gram negative bacilli.

They are inactivated by β -lactamase.

They are unstable to gastric acidity; therefore, they are taken **only parenterally**.

4- Talampicillin and carfecillin (prodrugs):

They are taken orally and changed by hydrolysis into ampicillin and carbenecillin respectively.

5- Ureido-penicillins (mezlocillin, azlocillin, and piperacillin):

They have a broad spectrum including salmonella, pseudomonas, and negative cocci.

They are taken by i.v. route.

6- Amidino-penicillin:

Mecillinam has the same spectrum as ureido-penicillins.

Pivmecillinam is a prodrug changing to Mecillinam and can be taken orally.

7- Anti-staph penicillins: oxacillin, cloxacillin, fluxacillin, flucloxacillin, nafcillin and dicloxacillin:

They have a narrower spectrum but are stable to gastric acidity and β -lactamase.

They can be taken orally.

N.B.: **Methicillin** is the first preparation in this group. It is not used nowadays due to its nephrotoxicity.

N.B.: Oxacillin or **Methicillin Resistant Staph Aureus (ORSA or MRSA)** do not respond to other β -lactams because they acquire penicillin-binding proteins with low affinity for β -lactams, but they respond to vancomycin or rifampicin.

c) Penicillin Combinations:

1- Ampicillin (broad spectrum) + cloxacillin (β -lactamase resistant) (*Ampiclox*).

Ampicillin (broad spectrum) + dicloxacillin (β -lactamase resistant) (*Cloxapen*).

Ampicillin (broad spectrum) + flucloxacillin (β -lactamase resistant) (*Ampiflux*).

Ampicillin (broad spectrum) + sulbactam (β -lactamase inhibitor) (*Unasyn, Ampictam, Sigmacyl, Sulbin, Synerpen, or Unictam*).

2- Amoxicillin (broad spectrum) + clavulanic acid (β -lactamase inhibitor) (*Augmentin, Curam, E-Moxclav, Hibiotic, Klavox, Megamox, or Magnabiotic*).

Amoxicillin (broad spectrum) + dicloxacillin (*Amoclox*).

Amoxicillin (broad spectrum) + fluxacillin (*Amoflux, Amofluxin, Famox, Flumox, Flucamox, Hiflucil, or Miclox*).

3- Piperacillin + tazobactam (β -lactamase inhibitor) (*Tazocin*).

4- Probenecid: decreases the renal tubular secretion of penicillin; therefore, it is used to increase the latter plasma level.

Cephalosporins and Cephamycins

Chemical Structure:

They are 7- amino cephalosporanic acid nucleus derivatives.

Mechanism of Action: As above.

Spectrum: As above.

Pharmacokinetics:

They are lipophobic drugs.

Absorption:

- Some members are absorbed orally while most of them are taken parenterally.

Distribution:

- Agents of the first and second generations cannot cross blood brain barrier while third generation agents (except cefoperazone) can cross and thus are used in meningitis.

Elimination:

- They are **excreted mainly by the kidney**. Their doses are adjusted in case of renal dysfunction.

- Cefoperazone and Ceftriaxone are excreted mainly in the bile; therefore, they can be used in biliary infection and in patients with renal dysfunction.

Uses:

1- Staph infection in patients resistant or sensitive to penicillin.

2- Respiratory, urinary, and biliary tracts infections.

3- Anaerobic infections.

4- Meningitis by third generation cephalosporins.

5- Chemoprophylaxis: heart valves, biliary tract and neurosurgery.

Adverse Effects:

1- **Hypersensitivity reactions:** There is cross-allergy with penicillins; therefore, they are avoided in patients with hypersensitivity to penicillins.

2- **Resistance:** There is a cross resistance with penicillins; therefore, they are avoided in penicillin-resistant infections.

3- **Irritation:** • Gastrointestinal upset as nausea, vomiting, and diarrhea (due to disruption of normal balance of intestinal flora) with oral routes especially agents that are incompletely absorbed orally.

• Painful on injection via i.m. route.

• Thrombophlebitis with i.v. route.

4- **Nephrotoxicity:** especially if used with aminoglycosides.

5- **Due to their broad spectrum action:** • Super-infection.

• Avitaminosis B and K.

6- **Cefoperazone, cefotetan, and cefmetazole** cause:

• Platelet dysfunction and hypo-prothrombinemia resulting in bleeding (avoided by vitamin K).

• Intolerance to alcohol resulting in disulfiram-like reaction.

Preparations:

First Generation	Second Generation	Third Generation	Fourth Generation
Spectrum <ul style="list-style-type: none"> Gram positive cocci (strep and staph). Some gram negative organisms (E coli and Klebsiella). 	Spectrum: <ul style="list-style-type: none"> Less active on gram positive than the first generation. Extended spectrum on gram negative organisms. Cephameycins: aerobic and anaerobic gram negative bacilli. 	Spectrum: <ul style="list-style-type: none"> As the second generation but more active against resistant gram negative organisms e.g., pseudomonas. 	Spectrum: <ul style="list-style-type: none"> Similar to the third generation.
Agents: <ul style="list-style-type: none"> Cephalexin (Cephalexin, Ceporex, Keflex, Neocef, or Cephaxin): it is the first oral cephalosporin. It is used in upper respiratory and urinary tract infection. Cefazolin (Cefamezin, Cefazolin, Totacef, or Zinol) (parenteral): used in surgical prophylaxis (the first choice) and in orthopedic surgery because it penetrates the bone well. Cefadroxil (Biodroxil, Cephradrol, CuriSafe, Duricef, Ibdroxil, or Longicef): oral/ 12 hours. Cephadrine (Cefadrine, Cephradine, Farcocef, Ultracef, or Velosef): oral, i.v., and i.m. Cephapirin (Cefatrexyl). 	Agents: <ul style="list-style-type: none"> Cefuroxime (Ceroxim, or Zinnat): used in community acquired pneumonia due to H. influenza. Cefaclor (Bacticlor, Ceclor, Cefaclor, or Serviclor): oral. Cefamandole: i.v. Cephameycins such as Cefoxitin Cefotetan, and Cefmetazole: used parenterally in mixed anaerobic infections including B. fragilis e.g., peritonitis. 	Agents: <ul style="list-style-type: none"> Cefoperazone (Cefazone, Cefobid, or Peracef). Cefixime (Ximacef). Cefprozil (Cefzil) Cefotaxime (Claforan, Cefaxim, Cefotax, Ceforan, Foxime or Cefotax). Moxalactam. Cefpodoxim (Cepodem, or Orelox) Ceftriaxone (Cefaxone, Cefotrix, Ofraamax, Rociphen, or Triaxone): with the longest $t_{1/2}$, good bone penetration, 40% excreted in the bile and thus used in biliary infection and used in gonorrhea (single injection) and typhoid (resistant cases) <ul style="list-style-type: none"> - They are used in severe infections. - They can cross blood brain barrier so they are used in meningitis. 	Agent: <ul style="list-style-type: none"> Cefepime (Maxipime). Cefpirome (Cefrom). Ceftazidime (Cefzim, Cetazime, Fortum, or Kefadim) <ul style="list-style-type: none"> They are taken parenterally. It can cross blood brain barrier.

Other β -Lactam Antibiotics

1) Carbapenems

1- **Imipenem** (Tienam with cilastatin)

only intravenously)

Spectrum:

It is the **broadest spectrum β -lactam**, effective against gram positive, negative and anaerobes. It is resistant to β -lactamase.

Side Effects:

- There is cross-allergy with penicillin.
- It is metabolized in the kidney to inactive nephrotoxic metabolites; therefore, it should be given with cilastatin to inhibit renal metabolism.
- There is increased risk of convulsions; therefore, it is not used in meningitis.

2- Meropenem (Meronom) and Ertapenem:

They are similar to Imipenem with less risk of convulsions and less renal metabolism thus no need for cilastatin.

II) Monobactams**Aztreonam (Azactam)**

Spectrum: (intravenously and intramuscularly)

It has a narrow spectrum, effective against aerobic gram negative organisms (as aminoglycosides).

It is resistant to β -lactamase.

Side Effects:

Unlike aminoglycosides, it is not nephrotoxic or ototoxic.

III) β -Lactamase Inhibitors**Clavulanic Acid and Sulbactam****Action:**

They irreversibly inhibit β -lactamase protecting antibiotics inactivated by it. They do not have significant antibacterial action; therefore, they should be combined with more active antibiotics.

Combination:

- Cefoperazone + sulbactam (*Sulperazone*)
- See above for other combinations.

Vancomycin (Vancocin)

Mechanism of Action: as above.

Pharmacokinetics:

They are lipophobic.

- It is not absorbed orally; therefore, it is given by i.v. infusion. It is used locally orally in pseudo-membranous colitis as below.
- It is excreted by the kidneys; therefore, the dose should be adjusted in renal dysfunction.

Uses:

1- **Staph resistant to penicillin (ORSA or MRSA):** it is the drug of choice e.g., severe staph pneumonia, endocarditis, and osteomyelitis.

2- Severe staph infections in **patients allergic to penicillins or cephalosporins.**

3- **Antibiotic-induced Pseudo-membranous colitis:**

It occurs after antibiotic use as with clindamycin and other broad spectrum antimicrobials such as tetracycline, co-trimoxazole, and chloramphenicol. These antibiotics kill intestinal flora resulting in flourishing of *Clostridium difficile* (gram positive anaerobe). It is given orally where it is not absorbed orally but acts locally.

This condition is also treated by metronidazole, and cholestyramine to bind toxins.

Side Effects:

- 1- Fever, chills, rigors, and phlebitis.
- 2- Shock with rapid infusion: this causes **red man syndrome** (due to histamine release). It is avoided by slow infusion and pretreatment with antihistaminics.
- 3- Ototoxicity.
- 4- Nephrotoxicity.

Bacitracin

Mechanism of Action: as vancomycin.

Spectrum: it is effective against gram positive organisms.

Uses:

It is restricted to topical application because it is potentially nephrotoxic.

Inhibitors of Protein Synthesis

They include: tetracycline, aminoglycosides, macrolides, chloramphenicol, and clindamycin.

Tetracyclines

Mechanism of Action: as above.

Spectrum: as above.

Pharmacokinetics: It is partially lipophilic and lipophobic

Absorption:

It is partially absorbed orally. Absorption is decreased by food due to formation of non-absorbable chelates of tetracycline with Ca^{++} , Mg^{++} , Al^{+++} (in antacids), and iron.

Distribution:

- They partially cross blood brain barrier in insufficient amounts to manage meningitis.
- They cross placenta and become concentrated in bones and teeth resulting in deformities.

Elimination:

- They are partially metabolized in the liver where the drugs and their metabolites are excreted in the bile undergoing enterohepatic circulation especially doxycycline.
- They are partially excreted in the urine; therefore, tetracyclines are contraindicated in renal dysfunction except doxycycline which is eliminated mainly in the bile.

Uses:

- 1- Broad spectrum antibiotic:
 - Amebiasis and brucellosis.
 - Acne.
 - Biliary infection (doxycycline and minocycline).
 - Chlamydial infections.
 - Cholera (doxycycline).
 - Mycoplasma pneumonia.
 - Gonorrhea and syphilis.
 - Meningococcal carriers (minocycline as it is concentrated in the saliva).
 - Rickettsial infection.
 - 2- Demeclocycline is used in treatment of syndrome of inappropriate secretion of antidiuretic hormone by antagonizing the effect of antidiuretic hormone on renal tubules.
- Adverse Effects:**
- 1- Gastrointestinal upset: nausea, vomiting, diarrhea, and epigastric pain as it is irritant and partially absorbed. This is decreased if it is taken with food.
 - 2- Chelation of:
 - Ca^{++} resulting in bone and teeth hypoplasia, discoloration and deformity. So it is contraindicated during pregnancy, lactation and in pediatrics less than 8 years.
 - Fe^{++} resulting in decreased absorption of iron.
 - Al^{+++} resulting in decreased absorption of aluminum.
 - 3- Super-infection with Candida, C. difficile, or resistant Staph in intestine.
 - 4- Avitaminosis B and K.
 - 5- Hypersensitivity reactions.
 - 6- Resistance.
 - 7- Photosensitivity of the skin to sun light.
 - 8- Anti-anabolic action.
 - 9- Hepatotoxicity in patients with renal failure or pregnancy.
 - 10- Fanconi-like syndrome: kidney damage due to toxic metabolites with outdated tetracyclines. So, tetracyclines are contraindicated in patients with renal impairment.

Preparations:

- 1- Tetracycline (*Hostacycline, Micycline, Tetracid, or Tetracycline*): short acting, 60% absorbed orally, 250 mg orally/6 hours and ampoules 100 mg.
- 2- Oxytetracycline (*Oxytetracid or Oxytetryne*).
- 3- Chlortetracycline: 30 % is absorbed orally resulting in more super-infection.
- 4- Demeclocycline: intermediately acting.
- 5- Doxycycline (*Doxy, Doxymycin, Farcodoxin, Tabocine, Tolexine, or Vibramycin*).
- 6- Minocycline.

Both 6 and 7 are long acting and are mainly lipophilic and 90% is absorbed orally.

Aminoglycosides

Mechanism of Action: see above.

Spectrum:

- Negative bacilli especially amikacin (tuberculous bacilli, *Hemophilus influenzae*, *Shigella*, *Pseudomonas*, *E. coli*, and *Proteus*).
- Positive cocci (staphylococci especially gentamycin, streptococci, pneumococci).
- Aerobic organisms.

They are ineffective against anaerobes

Pharmacokinetics: They are lipophobic.

Absorption: They are not absorbed orally; therefore, they are given parenterally.

Distribution: They do not cross blood brain barrier even when meninges are inflamed.

They are concentrated in the kidneys and ears resulting in nephrotoxicity and ototoxicity.

Elimination: They are excreted unchanged by the kidney; therefore, their doses should be decreased with renal impairment.

Uses:

They relatively have serious side effects; therefore, they should be used only in severe infections.

- 1- Complications of influenza such as pneumonia.
- 2- Bacillary dysentery, gastrointestinal infections, and peritonitis.
- 3- Septicemia.
- 4- Complicated urinary tract infections.
- 5- Staph infection as skin infection, abscess, otitis media, osteomyelitis, and upper respiratory tract infection in patients sensitive or resistant to penicillin.
- 6- Tuberculosis especially by **streptomycin**.
- 7- Sterilization of the bowel before surgery and during hepatic coma by **neomycin** orally. It is not absorbed and acts locally. It also acts locally in infected wounds. It is too toxic for systemic use resulting in nephrotoxicity.
- 8- Resistant infections are treated by **amikacin** and **netilmicin**.

Side Effects:

- 1- **Nephrotoxicity:** acute tubular necrosis especially with dehydration, elderly patients, large doses, prolonged duration, and usage of other nephrotoxic drugs.
- 2- **Ototoxicity:** especially with concurrent use of loop diuretics or quinidine.
Cochlear insult: tinnitus and deafness especially by kanamycin, neomycin, and amikacin.
Vestibular insult: vertigo especially by streptomycin and gentamycin.
- 3- **Muscle relaxation:** they produce muscle relaxation especially with large doses as they decrease acetylcholine release.
- 4- **Hypersensitivity reactions:** as contact dermatitis with topical neomycin.
- 5- **Resistance.**
- 6- **Drug interactions:**
 - With penicillin outside the body, inactivation occurs.
 - With skeletal muscle relaxants, potentiation of muscle relaxation occurs.
 - With loop diuretics, increased risk of ototoxicity occurs.
 - With cephalosporins, increased risk of nephrotoxicity occurs.

Preparations:

- 1- **Streptomycin:** 1 gm/day i.m.
- 2- **Dihydro-streptomycin:** is used mainly locally as a skin ointment or orally in bacillary dysentery or in sterilization of bowel before surgery (not systemically).
- 3- **Gentamycin** (*Epigent*, *Garamycin*, *Gentamycin*, *Refobacin*, or *Rigaminol*): is usually used in combination with penicillin in a dose of 1 mg/kg i.v. because:
 - Penicillin destroys cell wall allowing gentamycin to penetrate. Both are bactericidal.
 - Both complete the spectrum for each other as penicillin is active against most of the spectra except gram negative bacilli against which gentamycin is active. Therefore, they are used in severe infections but with follow up with creatinine clearance.
- 4- **Tobramycin** (*Nebcin*, *Tobcin*, or *Tobracin*): less toxic than gentamycin.
- 5- **Amikacin** (*Amikin*, or *Likacin*).
- 6- **Neomycin** (*Neomycin*).

7- Netilmicin.

8- Miocamycin (*Miocamen*).

9- **Paromomycin**: effective against Amebiasis.

N.B.: **Spectinomycin**:

- It is structurally related to aminoglycosides.

- It is used in resistant cases of gonorrhea in patients allergic or resistant to penicillins by a deep single i.m. injection.

Macrolides

They include - Erythromycin.

- Clarithromycin

- Lincomycin.

- Clindamycin.

- Azithromycin.

- Roxithromycin.

- Spiramycin.

Erythromycin (*Erythromycin, Eryped, Erythrin, or Erythrocin*)

Mechanism of Action: see before.

It is bacteriostatic at low doses and bactericidal at high doses.

Spectrum and Uses:

It is effective against chlamydia, mycoplasma, spirochetes, gram positive cocci and bacilli.

They are used as an alternative to penicillin and tetracyclines especially for:

• Patients allergic to penicillins.

• Urogenital chlamydia infection during pregnancy.

• Mycoplasma chest infection in pediatrics as tetracyclines are contraindicated.

Pharmacokinetics:

Absorption:

It is destroyed by gastric juice; therefore, it is given as enteric coated tablets. Food decreases its absorption.

Clarithromycin is not destroyed by gastric acidity.

Distribution:

It poorly crosses the blood brain barrier.

Elimination:

It is metabolized in the liver and acts as an enzyme inhibitor for other drugs.

Side Effects:

1- Gastrointestinal upset as epigastric pain, nausea, and vomiting.

2- Cholestatic jaundice by estolate salts.

3- Reversible ototoxicity.

4- Thrombophlebitis on i.v. injection.

5- Hypersensitivity reactions.

6- Drug interactions:

• It acts as an enzyme inhibitor, increasing the level of theophylline, warfarin, carbamazepine, and terfenadine resulting in arrhythmias.

• It inhibits intestinal flora that inactivate digoxin resulting in increased level of serum digoxin.

N.B.: Erythromycin + Trimethoprim (*Erythroprim or Primomycin*).

Erythromycin + Sulfisoxazole (*Pediazole*).

Other New Macrolides

1- **Azithromycin** (*Azalide, Azrolid, Aziwok, Azomycin, Xithrone, Zisrocine, Zithrokan, or Zithromax*).

2- **Clarithromycin** (*Claribiotic, Clarithro, Klacid, or Klarimix*).

3- **Roxithromycin** (*Roxicin, or Roxid*).

4- **Lincomycin** (*Lincocin*).

5- **Telithromycin** (*Ketek*).

6- **Spiramycin** (*Rovac, Rovapex, Rovamycin, Spiracin, Spirex, Spiramycin, or Unispira*).

Spiramycin + Metronidazole (*Spirazole or Rodogyl*).

They are - semi-synthetic derivatives of erythromycin.

- stable with gastric acidity and have better gastrointestinal absorption.

- with long half lives allowing the use of a single daily dose.

Azithromycin is more effective against gram negative organisms and chlamydia and less effective against gram positive organisms than erythromycin.

Clindamycin (Clinacyn, Clindacine, Clindam, Dalacin-C, or Mepaclind)

It is similar to other macrolides.

Mechanism of Action: see above; it is bacteriostatic.

Spectrum:

It is effective against **anaerobic infections** and gram positive organisms (staph and strept).

Uses:

- Bone and joint infection due to good penetration.
- Intra-abdominal sepsis.

Side Effects:

- Pseudo-membranous colitis caused by clostridium difficile. It is treated by vancomycin.
- Hypersensitivity.
- Hepatic dysfunction.

Chloramphenicol (Chloramphenicol, Cidocetine, Memcocetin, or Miphenicol)

Mechanism: as above.

Spectrum: broad spectrum affecting bacteria and rickettsia.

Pharmacokinetics:

It is lipophilic drug.

Absorption:

It is completely absorbed orally; therefore, it can be taken orally.

Distribution:

It is easily distributed all over the body and crosses the blood brain barrier.

Elimination:

It is metabolized in the liver and excreted by the kidneys.

Uses:

- 1- Typhoid fever (not the carrier). It is replaced now by quinolones.
- 2- Cerebrospinal meningitis e.g., H. influenza, in combination with penicillins.
- 3- Eye infection (topically).
- 4- Anaerobic infections.
- 5- Complicated influenza infection.

Side Effects:

- 1- Hypersensitivity reactions.
- 2- Resistance.
- 3- Gastrointestinal upset and super-infection.
- 4- **Bone marrow depression** especially agranulocytosis. It is either dose dependent or dose independent (idiosyncratic reactions).
- 5- **Grey baby syndrome:** decreased metabolism of chloramphenicol due to immaturity of the liver especially in neonates and premature babies due to decreased activity of glucuronyl transferase. This increases the level of chloramphenicol resulting in cardiovascular collapse, grey stools, toxic face, up to death in 40% of cases; therefore, the dose should not be increased more than 50 mg/kg.
- 6- Avitaminosis B and K.
- 7- Optic nerve damage.
- 8- Hepatic dysfunction.
- 9- It acts as an enzyme inhibitor increasing the level of warfarin, phenytoin, and oral hypoglycemics levels if they are taken simultaneously.

Another related drug: Thiamphenicol (Thiophenicol)

Inhibitors of Nucleic Acid Synthesis

They include • Quinolones.

• Rifampicin.

Quinolones

Mechanism: see above.

Pharmacokinetics:

They are lipophilic. They are well absorbed orally and widely distributed all over the body and excreted mainly by the kidneys.

Preparations:**A) Non-Fluorinated Quinolones:****First Generation: Nalidixic Acid** (*Nalidram*)

- It is 90% bound to plasma proteins so the free active drug is minimal; therefore, it is not used in systemic infections.
- It is used mainly in urinary tract infections with gram negative bacilli.
- Resistance is easily developed.

B) Fluorinated Compounds:

- They are potent and can be used in systemic infections.

Second Generation:

- **Norfloxacin** (*Epinor, Noracin, Neofloxin, or Norbactin*): is used mainly in urinary tract infections as it does not achieve systemic levels.
- **Ciprofloxacin** (*Ciprofloxacin, Bactiflox, Ciprobay, Ciprinol, Ciprocine, Ciprofar, Cipromax, Ciproquin, Mifoxin, Ranicef, or Serviflox*): is the most potent.
- **Ofloxacin** (*Kiroll, Oflicin, Ofloxacin, Ofloxin, Tarivan, Tarivid, or Tariflox*).
- **Pefloxacin** (*Globacin, Peflox, Pelox, or Sparatec*).
- **Gatifloxacin** (*Floxin, Gatilox, or Tequin*).
- **Sparfloxacin** (*Parox, Spara, or Sparcin*).

They are effective mainly against aerobic gram negative organisms such as *Pseudomonas*, *E. coli*, *H. influenzae*, *Proteus*, *Salmonella*, and penicillinase-producing gonococci, but weak against gram positive organisms and are ineffective against anaerobes.

Third Generation:

- **Levofloxacin** (*Alfacef, Lee-Flox, Levoxin, Larivex, Levanic, Tavanic, Unibiotic, or Venaxan*).
- **Lomefloxacin** (*Lomeflox, Lomex, or Lomoxen*).

It is effective against gram negative organisms with greater action on gram positive such as pneumococci than ciprofloxacin.

Fourth Generation:

- **Moxifloxacin** (*Avalox*)
- **Clinafloxacin**: It is more potent against anaerobic infections.

It is effective against gram negative organisms but less than ciprofloxacin (poor against *Pseudomonas*). It is effective against gram positive cocci especially *Streptococcus pneumoniae* and some staph organisms. It is active against anaerobes.

Uses:

- 1- Urinary tract infections.
- 2- Respiratory tract infections resistant to β -lactams and atypical pneumonia due to chlamydia, mycoplasma, legionella especially by Levofloxacin and Moxifloxacin.
- 3- Bone and soft tissue infections.
- 4- Typhoid fever.
- 5- Infective diarrhea and other gastrointestinal infections. Ciprofloxacin is the first choice in empirical treatment.
- 6- Gynecological infections.
- 7- Gonorrhea especially by Ofloxacin and Levofloxacin.
- 8- Resistant tuberculosis.

Side Effects:

- 1- Hypersensitivity reactions.
- 2- Gastrointestinal upset.
- 3- Neurological affection such as headache, dizziness, insomnia, and convulsions.
- 4- Hepatic dysfunction.
- 5- Inhibition of cartilaginous growth especially in pediatrics less than 18 years old.
- 6- Teratogenicity.

Therefore, they are contraindicated during pregnancy, lactation, and in pediatrics.

- 7- Resistance.
- 8- Phototoxicity.
- 9- Drug interactions:
 - They act as enzyme inhibitors increasing the level of warfarin and theophylline.
 - They prolong QT interval resulting in arrhythmias especially with hypokalemia.
 - Cations in antacids decrease quinolones absorption.

Rifampicin (Rifampin) (*Rifactine, Rifadin, Rifam, Rifampicin, Rimactane, Rifocin, or Rifamox*)

Mechanism: see above.

Spectrum:

It has a broad spectrum effect against MRSA, and mycobacteria as tuberculosis, and leprosy. It also has antiviral action.

Pharmacokinetics: It is lipophilic.

Absorption:

- It is well absorbed orally.

Distribution:

- It is widely distributed all over the body including the blood brain barrier, body fluids, and tuberculous cavities.

Elimination:

- It is metabolized by the liver. It acts as a potent enzyme inducer.
- It is excreted mainly in the bile resulting in enterohepatic recycling with minimal excretion by the kidneys.

Uses:

- 1- Mycobacteria such as tuberculosis (all types as open, closed fibrous, caseous, meningeal, pleural, and peritoneal tuberculosis) and leprosy.
- 2- MRSA infections.
- 3- Meningitis (meningococcal or H. influenza) for active management and prophylaxis.
- 4- Brucellosis (in combination with doxycycline "the first choice").

Side Effects:

- 1- Hypersensitivity reactions as skin rash.
- 2- Resistance which is rapid due to modification of DNA-dependent RNA polymerase by chromosomal mutation. There is no cross resistance with other anti-tuberculous drugs.
- 3- Super-infection and gastrointestinal upset.
- 4- Renal and hepatic dysfunction and jaundice.
- 5- It acts as a **potent enzyme inducer**.
- 6- Bone marrow depression with thrombocytopenia, leukopenia, and anemia.
- 7- **Red discoloration of the urine**, tears, sputum, and contact lenses due to its metabolites.
- 8- An influenza like syndrome such as malaise, headache, and fever with large doses.

Inhibitors of Metabolic Pathways (Folate Antagonists)

Sulfonamides

Mechanism: see above. They affect only the bacterial cells as human cells utilize already-formed folic acid.

Spectrum: see above.

Pharmacokinetics:

They are lipophilic as before. Their metabolites are nephrotoxic.

Uses and Preparations:

- 1- **Sulfadiazine** is used for meningitis (systemic) and burns (topical silver salts).
- 2- **Succinyl sulfathiazole** and **phthalyl sulfathiazole** are non-absorbable and are used in bacillary dysentery, gastrointestinal infection and to sterilize the bowel before surgical procedures.
- 3- **Sulfasalazine** is used for ulcerative colitis.
- 4- **Sulfacetamide** is used for eye infections (topically).
- 5- **Combination of sulfadoxine and pyrimethamine** is used in malaria infections.
- 6- **Combination of sulfamethoxazole (400 mg) and trimethoprim (80 mg) (Cotrimoxazole)** (*Septtrin, Bacterim, Chemotrim, Cotril, Septazole, Sutrim, Entrim, Supristol, or Sutaprim*) is used in bacterial infections as:
 - Urinary tract infections, gonococcal urethritis and prostatitis.
 - Salmonella and Shigella infections.
 - Respiratory tract infections due to H. influenza and S. pneumoniae.
 - Biliary tract infections.

This combination has advantages of synergistic action and delayed onset of resistance.

Side Effects:

1- **Nephrotoxicity and crystalluria:** due to precipitation of their acetylated metabolites in the acidic medium of the urine resulting in crystalluria (micro-crystals) and nephritis with proteinuria and hematuria. This is avoided by increased fluid intake and alkalinization of the urine.

2- **Hypersensitivity reactions.**

3- Hepatic dysfunction as they are lipophilic.

4- **Kernicterus:** especially in premature babies because sulfonamide derivatives displace bilirubin from the plasma protein binding sites resulting in increased serum free level of bilirubin which passes through the blood brain barrier to the brain causing central nervous manifestations such as convulsions.

5- **Hematological side effects:**

• Bone marrow depression causing granulocytopenia and thrombocytopenia.

• Hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency.

6- Resistance.

7- Drug interactions: they displace other drugs from their binding sites on the plasma proteins increasing the level of these drugs as **oral hypoglycemics and anticoagulants.**

8- **Side effects of trimethoprim:**

• Megaloblastic anemia due to folic acid deficiency.

• Granulocytopenia and leucopenia.

• Super-infection.

• Avitaminosis B and K.

N.B.: Side effects of cotrimoxazole include these of sulfonamides and trimethoprim.

Clinical Choices of Antibacterial Agents

General Precautions:

• Bactericidal drugs should be given, with avoiding bacteriostatic drugs, in the following conditions:

- Agranulocytosis.
- Infective endocarditis.
- Carriers.
- Immunosuppressed and low-resistant patients.
- Geriatric patients.

• The doses should be individualized according to the age, body weight, and renal conditions.

• Culture and sensitivity tests should be done.

• Appropriate empiric therapy for serious infections should be determined by likely organisms, taking into account known community and hospital infection, and resistance patterns.

Different Disease Conditions

■ Antimicrobials Against Penicillinase-Producing Staph

- 1- Penicillinase resistant penicillins as cloxacillin.
- 2- Second and third generation cephalosporins.
- 3- Macrolides as erythromycin and clindamycin.
- 4- Cotrimoxazole.
- 5- Quinolones as ciprofloxacin.
- 6- Rifampicin.

■ Antimicrobials Against MRSA

- 1- Vancomycin.
- 2- Rifampicin.

■ Antimicrobials Against Bone Infections

- 1- Penicillinase resistant penicillins as cloxacillin.
- 2- Clindamycin.
- 3- Cephalosporins as cefazolin, cefalexin, or ceftriaxone.
- 4- Ciprofloxacin.
- 5- Rifampicin.

■ Antimicrobials Against Pneumonias

- 1- Penicillins.
- 2- Cephalosporins.
- 3- Quinolones.
- 4- Antimicrobials against anaerobic infections.
- 5- Antifungal treatment.

■ Antimicrobials Against Gram Negative Organisms e.g., Pseudomonas

- 1- β -Lactam antibiotics as anti-pseudomonas penicillins.
- 2- Third and fourth generation cephalosporins.
- 3- Quinolones.
- 4- Monobactam (aztreonam) or Imipenem.
- 5- Aminoglycosides as gentamycin or tobramycin.

■ Antimicrobials Against Meningitis

- 1- Third and fourth generation cephalosporins.
- 2- Chloramphenicol.
- 3- Penicillins.

- 6- Vancomycin.
- 7- Gentamycin.
- 8- Tobramycin.

■ **Antimicrobials Against Bacterial Endocarditis**

- 1- Penicillinase resistant penicillins or vancomycin and gentamycin.
- 2- Cephalosporins.

■ **Antimicrobials Against Anaerobic Infections**

- 1- Metronidazole.
- 2- Clindamycin.
- 3- Cefoxitin.
- 4- Chloramphenicol.
- 5- Imipenem.

■ **Antimicrobials Against Typhoid Fever**

- 1- Chloramphenicol (for active cases).
- 2- Quinolones, amoxicillin, ciprofloxacin, or co-trimoxazole (for carriers).
- 3- Ceftriaxone (for resistant cases).

■ **Antimicrobials Against Tuberculosis**

- 1- First line: - Rifampicin - Isoniazid (INH) - Pyrazinamide - Ethambutol - Streptomycin.
- 2- Second line: Ceftriaxone - Fluoro-quinolones - Aminosalicylic acid - Cycloserine - Ethionamide - Capreomycin - Clarithromycin.

■ **Antimicrobials Contraindicated in Infants and Children**

- 1- Tetracyclines: cause teeth and bone affection.
- 2- Chloramphenicol: causes grey baby syndrome.
- 3- Sulfonamides: cause Kernicterus.
- 4- Quinolones: cause arthropathy.

■ **Antimicrobials Against Urinary Tract Infections**

- 1- Cotrimoxazole.
- 2- Fluoro-quinolones.
- 3- Amoxicillin.
- 4- Rifampicin.

- 4- Rifampicin (in prophylaxis).
- 5- Sulfadiazine (in prophylaxis).

■ **Antimicrobials Against Brucellosis**

- 1- First choice drugs: doxycycline and rifampicin or aminoglycosides.
- 2- Second choice drugs: chloramphenicol and aminoglycosides or co-trimoxazole.

■ **Antimicrobials Against Biliary Tract Infections**

- 1- Cefoperazone.
- 2- Ceftriaxone.
- 3- Rifampicin.
- 4- Doxycycline.

■ **Antimicrobials Against Prostatic Infections**

- 1- Fluoro-quinolones.
- 2- Macrolides.
- 3- Trimethoprim.

■ **Antimicrobials Against Leprosy**

- 1- Rifampicin.
- 2- Dapsone: bacteriostatic, related to sulfonamides.
- 3- Clofazimine.

■ **Antimicrobials Used in Pregnancy**

- 1- Penicillins.
- 2- Cephalosporins.
- 3- Erythromycin.

■ **Antimicrobials Against Gonorrhea**

- 1- Penicillins.
- 2- Ceftriaxone.
- 3- Fluoro-quinolones (Ofloxacin and levofloxacin).
- 4- Spectinomycin (as a single dose).
- 5- Rifampicin.
- 6- Cephalosporins.
- 7- Tetracyclines.

Antiviral Drugs

Classification According to Mechanism: They decrease viral replication as follows:

- 1- Drugs decrease uncoating and virus penetration into the host cells (they have no virucidal actions): amantadine and γ globulins.
- 2- Drugs decrease DNA synthesis: acyclovir and idoxuridine.
- 3- Drugs decrease RNA synthesis: ribavirin and interferons.
- 4- Drugs decrease synthesis of late proteins (protease inhibitors): indinavir, saquinavir, ritonavir, and nelfinavir.
- 5- Drugs decrease assembly (maturation) and release of viral particles: rifampin.
- 6- Drugs inhibit reverse transcription (Nucleoside analogue reverse transcriptase inhibitors): zidovudine, didanosine, zalcitabine, stavudine, lamivudine.
- 7- Non-nucleoside analogue reverse-transcriptase inhibitors (interfere with the transcriptional activity of this enzyme by binding to it directly, downstream of the active catalytic site): nevirapine, delavirdine, and efavirenz.
- 8- Drugs inhibit integrase enzyme (which the virus needs for incorporation of its proviral DNA into the infected cell's chromosomal DNA) (integrase inhibitors): raltegravir.
- 9- Chemokine receptor 5 antagonists: maraviroc.
- 10- Neuraminidase inhibitors: as zanamivir and oseltamivir.

Amantadine: (*Adamine, Amantine, Amantadine, or PK-Merz*)

- Uses:
- Influenza A virus.
 - Treatment of Herpes zoster.
 - Parkinsonism (as it may augment dopaminergic activity).

Side effects: mainly on the central nervous system; headache, dizziness, seizures, and confusion.

Amantadine (*Rymanta*).

Ganciclovir: (*Cymevene*)

- Uses:
- in life-threatening cytomegalovirus infections in immuno-compromised patients.

Ribavirin: (*Panvirin, Rebetol, Riba, Ribavirin, Viracure, Virazole, or Virokan*)

Uses: It is active against a wide range of viruses including influenza type A, B, rubella, rhinovirus, viral hepatitis, and herpes simplex.

- Side effects:
- Cholestatic jaundice.
 - Anemia.

Acyclovir: (*Acyclovir, Cycloviral, Lovir, Novirus, Virin, or Zovirax*)

- Uses:
- Herpes simplex.
 - Epstein-Barr virus.
 - Herpes zoster.
 - Cytomegalovirus.

- Adverse effects:
- Gastrointestinal upset.
 - Kidney damage.
 - Local irritation

Famciclovir (*Famvir*): is an ester of acyclovir which is licensed for herpes zoster and herpes simplex.

Indinavir:

Uses: with zidovudine in acquired immune deficiency syndrome (AIDS).

- Side effects:
- Gastrointestinal upset.
 - Kidney damage.
 - Enzyme inhibition.

Zidovudine: (*Retrovir*)

Uses: AIDS.

- Side effects:
- Gastrointestinal upset.
 - Cholestatic hepatitis.
 - Bone marrow depression.

Lamivudine: (*lamidine or Zeffix*)

It is selective inhibitor of human immune deficiency virus type 1 and 2 (HIV-1 and HIV-2).

Uses: AIDS and hepatitis (in combination with other agents).

Interferons (IFN): (*Egyferon, Ismafron, Intron-A, Peg-Interon, Roferon, Rebif, or Reiferon*)

Mechanism: Interferons are cytokines (proteins) produced by intact or cultural cells in response to virus infections and they decrease viral replication. They are species specific. They are produced by genetic engineering (*E. coli*) e.g. INF δ , INF β , and INF γ .

- Uses:
- Chronic active hepatitis.
 - Genital warts.
 - Disseminated herpes.
 - AIDS.

- Side effects:
- Flu-like syndrome.
 - Headache and dizziness.
 - Hypotension and arrhythmias.
 - Gastrointestinal upset.
 - Alopecia.
 - Bone marrow depression.

IMMUNOSUPPRESSANT AGENTS

Categories of Immunosuppressant Agents used in Transplant Patients

1- Corticosteroids: were the first drugs to be used as immunosuppressive agents.

2- Calcineurin inhibitors such as • Cyclosporin A (by other authors ciclosporin A) (*Neoral* or *Sandimmune*).
• Tacrolimus (*Prograf*). It is used in cyclosporin-resistant acute rejection.

Cyclosporin selectively suppresses helper T cells (CD₄ lymphocytes) by inhibition of the production of interleukin II (IL-II) and other cytokines. IL-II is responsible for:

- Generation and proliferation of cytotoxic T cells which are responsible for graft rejection.
- Activation of B cells causing T cell dependent humoral responses.

3- Target of rapamycin inhibitors such as • Sirolimus (*Rapamune*).
• Everolimus.

4- Polyclonal antibodies such as • Antilymphocyte globulin (*Atgam*, *Thymoglobulin*).

5- Monoclonal antibodies such as • Interleukin 2 (IL-2) receptor blockers (CD25).

- Daclizumab (*Zenapex*).
- Basiliximab (*Simulect*).
- OKT3 (*Anti-CD3*, or *Monomurab*).

6- Purine synthesis inhibitors such as

- Azathioprine (*Imuran*): that is metabolized to an active form in the liver.
- Mycophenolate mofetil (MMF or *Cellcept*).

Side Effects

All immunosuppressant agents cause increased incidence of opportunistic infections and cancer.

1- Corticosteroids: Side effects are discussed above such as cushinoid appearance, hypertension, hyperglycemia, peptic ulcer disease, adrenal suppression, and osteoporosis.

2- Calcineurin inhibitors (cyclosporin or tacrolimus):

- Nephrotoxicity
- Hypertension and prolonged QT interval
- Hypercoagulability
- Hyperchloremic acidosis, hyperkalemia, hypomagnesemia, hypocalcemia, glucose intolerance
- Acute microvascular disease (similar to thrombocytopenic purpura).
- Hepatotoxicity
- Dysesthesia, headache, seizures, coarse tremors, coma
- Gingival hypertrophy

3- Target of Rapamycin inhibitors (sirolimus or everolimus):

- Mucocutaneous ulceration.
- Hypomagnesemia.
- Interstitial pneumonia.
- Hypokalemia.
- Impaired wound healing.
- Cytopenia.

4- Polyclonal antibodies:

- Pulmonary hypertension.
- Acute respiratory failure.
- Symptoms of cytokine release (fever, chills, dyspnea, wheezing, and chest pain).
- Leukopenia and thrombocytopenia.
- Bronchospasm.

5- Monoclonal antibodies:

a- Daclizumab and basiliximab:

- Gastrointestinal upset.

b- OKT3:

- Symptoms of cytokine release (fever, chills, dyspnea, wheezing, and chest pain).
- Leukopenia.

6- Purine Synthesis Inhibitors:

a- Azathioprine (*Imuran*):

- Cytopenia (especially if combined with allopurinol).
- Hepatitis.
- Viral warts.
- Malignancies of the skin.
- It antagonizes non-depolarizing muscle relaxants by its phosphodiesterase inhibiting action; so larger doses of muscle relaxants are needed.

b- Mycophenolate mofetil (MMF or *Cellcept*):

- Nausea, vomiting, diarrhea, and abdominal pain.
- Cytopenia (leukopenia, anemia, thrombocytopenia) or leukocytosis.
- Hypertension.

PHARMACOGENOMICS

Definitions

Pharmacogenetics: It describes the effect of genetic factors (genes) on drug kinetics (drug body interactions) and dynamics (drug receptor interactions).

Pharmacogenomics: It is the application of genomic technologies (whole-genome or individual gene changes) to drug discovery, pharmacokinetics and pharmacodynamics, pharmacological response, and therapeutic outcome.

Many authors consider this distinction unimportant and use the two interchangeably.

Pharmacogenetics (or pharmacogenomics) aim to understand the inherited basis for variability in drug response. It changes drug response from (one drug and dose fit all) to individualized predictive medicine or (the right drug with the right dose in the right patient).

Genomics: It is the study of the genome. This includes gene structure and function as well as control mechanisms, gene expression, gene-environment interactions and the wider implications of gene contribution to diseases.

The complete human genome consists of approximately 3 billion base pairs which encode approximately 30 000 genes.

Genetic Polymorphism: It is the presence of multiple discrete states for a particular trait, within a population, which has an inherited difference.

Single Nucleotide Polymorphism (SNP): It is a variation in the DNA sequence which occurs at a specific base.

Polymorphism is relatively common occurring in $\geq 1\%$ of the population, while mutations are less common, occurring in $< 1\%$.

SNP deletions, insertion, duplications and splice variants can cause RNA and protein changes; they are not inherited.

Pharmacogenetic Variability

It is either pharmacokinetic variability or pharmacodynamic variability.

I) Pharmacokinetic Variability:

It refers to variability in the amount of drug delivered to a receptor; otherwise known as drug disposition.

The variability occurs either in metabolism or transporter proteins.

A) Variability in Metabolism:

- Metabolism converts lipophilic (fat soluble) drugs to more polar (water soluble) molecules more amenable to renal excretion.

- Metabolism converts:

- An **inactive prodrug to an active** metabolite e.g., oxidation of inactive codeine to the more active metabolite morphine.

- An **active drug to an active** metabolite e.g., morphine conversion to morphine-6- glucuronide.

- An **active to an inactive** metabolite e.g., morphine to normorphine.

- or - An **active drug to a toxic** metabolite e.g., meperidine to normeperidine which can cause seizures.

- Metabolism is either phase I or phase II reactions.

Phase I Reactions or Metabolism

- It converts foreign substances such as drugs into water-soluble metabolites by a superfamily of drug metabolizing enzymes called cytochrome P450 enzymes (CYPs).

N.B.: **Cytochrome P450 Enzymes (CYPs):**

The classification of these enzymes is based upon their amino acid structure. CYP enzymes are found primarily in the liver (mainly), lungs, kidneys, gut, and brain.

- The **superfamily** of CYPs enzymes is grouped in **families** which are designated as CYP 1, 2etc. **CYP2** shares >40% in metabolism and is the most important.

- Each family is then grouped in **subfamilies** which are designated as CYP2A, B...etc. **CYP2A** shares in >55% and is the most important.

- Each **individual enzyme** in the subfamilies is then identified by a third number as **CYP2A6**.

- Each individual enzyme has **allelic variants** which are designated by an asterisk and number following the protein identifier as **CYP2A6*1**.

- The majority of drugs are metabolized in humans by CYPs1, 2, and 3 (mainly CYP2C, 2D6, and 3A).
- Mutations in genes of these enzymes produce either a poor metabolizer or an extensive metabolizer. Both cause variation in the effect of the drug metabolism.

Examples of enzyme variants:

a- Cytochrome P450 Enzymes (CYPs):

Enzyme	Metabolized Drugs	Variants (Mutations)
CYP2A6	Nicotine (smoking)	Some Chinese-Americans metabolize nicotine more slowly than whites or Latinos and have a lower incidence of lung cancers.
CYP2B6	Methadone, propofol, and ketamine	Some African-Americans have a mutation in this enzyme resulting in low enzyme activity and increasing drug activities.
CYP2C9	S-warfarin, phenytoin, COX-II selective inhibitors, diclofenac, and several NSAIDs.	Some patients have variants with decreased enzyme activities, resulting in increased drug actions e.g., life-threatening bleeding with warfarin. Therefore, adjusting the dose is very important to avoid complications.
CYP2C19	Diazepam, omeprazole, propranolol, barbiturates as hexobarbital.	Individuals are either: extensive metabolizers (most individuals) or poor metabolizers (5% Caucasians, 2% African-Americans, 20% Japanese, 15% Chinese).
CYP2D6	B-blockers (as metoprolol, propranolol and timolol), opioids (as codeine, tramadol, dextromethorphan, dihydrocodeine, hydrocodone, and oxycodone), many antiarrhythmics, antipsychotics, tricyclic antidepressants, serotonin reuptake inhibitors, and antiemetics (as 5HT ₃ antagonists).	<ul style="list-style-type: none"> • Individuals are extensive metabolizers (mainly), poor metabolizers (5% Caucasians, 2% African-Americans), or ultra-rapid metabolizers (20% Ethiopians, 7% Spanish, 1% Scandinavians). Ultra-rapid metabolizers require higher doses of the drugs.
CYP2E1	Volatile anesthetics	This explains some of the differences in outcome from anesthesia as postoperative nausea, vomiting, and jaundice.
CYP3A4	Opioids, benzodiazepines, local anesthetics, calcium channel blockers, and immuno-suppressants.	Some individuals are poor metabolizers. It is the most quantitatively abundant CYP in the human liver, accounting for 30-60% of total CYP. It is also the predominant CYP in the human intestine.
CYP3A5	It is similar to CYP3A4 and metabolizes many but not all CYP3A4 substrates. It is often with decreased activity	Some individuals have high activity of both CYP3A4 and CYP3A5, so the drugs metabolized with them have a greater metabolism.

b- Non-CYP-450 enzymes:

Enzyme	Metabolized Drugs and Variants (Mutations)
Carboxyl-esterases	<p>They are found in the liver in great amounts, and also in gut, brain and blood. There are two variants of these enzymes:</p> <ul style="list-style-type: none"> • hcE-1 catalyzes the hydrolysis of: <ul style="list-style-type: none"> - cocaine to benzoyl-ecgonine, - meperidine to meperidinic acid (the major route of metabolism), and - heroin (3, 6-diacetylmorphine) to 6-monoacetylmorphine (an active metabolite). • hcE-2 catalyzes the hydrolysis of: <ul style="list-style-type: none"> - heroin to both 6-monoacetylmorphine and then to morphine. - irinotecan (an anticancer agent) into an active metabolite. <p>There are many variants of these enzymes.</p>
Plasma (pseudo) cholinesterase	There are many variants which explain the prolongation of the action of succinylcholine (see chapter of pharmacology of anesthesia).
Acetyl-cholinesterase	<ul style="list-style-type: none"> • It is found mainly in the neuromuscular junction and hydrolyses acetylcholine. • It is also found in erythrocytes and metabolizes esmolol and remifentanyl, so deficiency of pseudo-cholinesterase does not affect their metabolism.

Phase II Reactions or Metabolism

- It converts non-soluble drugs into water-soluble metabolites (which are rapidly excreted), by:
 - Methylation: addition of methyl group.
 - Glucuronidation: addition of glucuronic acid
 - Sulphation: addition of sulfur.
 - Acetylation: addition of acetyl group.

• Examples:

Enzyme	Metabolized Drugs and Variants (Mutations)
Uridine diphosphate-glucuronosyl transferase (UGT)	<p>There are two isoforms:</p> <ul style="list-style-type: none"> • UGT1A: metabolizes phenols as propofol (UGT1A9), and bilirubin. UGT1A has many variants as UGT1A1 that has much lower enzyme activity resulting in mild hyper-bilirubinemia (Gilbert's syndrome). • UGT2: metabolizes bile, steroids, midazolam, opioids (UGT2B7) such as morphine (to morphine 6-glucuronide), codeine, naloxone, nalorphine, buprenorphine, oxycodone, and hydromorphone.
Glutathione-S-transferase (GST)	<ul style="list-style-type: none"> • It catalyses the reaction of the glutathione with many drugs and toxins. It is primarily a defensive system for detoxification. • It has a very minor role in metabolism of anesthetic drugs except in the metabolism of the sevoflurane degradation product "compound A".
N-acetyl-transferase (NAT)	<ul style="list-style-type: none"> • There are two isoforms NAT₁ and NAT₂. • NAT is of great historical significance because it has been the first enzyme where a genetic variant has been discovered (fast- and slow acetylators). • It causes acetylation of many drugs as isoniazid (inactive metabolites), procainamide (active metabolites), hydralazine, sulphonamide, and many drugs (carcinogens). • Slow acetylators require smaller doses than fast acetylators and they are susceptible to more side effects than fast acetylators such as isoniazid-induced hepatotoxicity and neuropathy, hydralazine or procainamide-induced lupus-like syndromes and sulphonamide-induced hypersensitivity.
Thiopurine S-methyl transferase	<ul style="list-style-type: none"> • They cause methylation of azathioprine and 6-mercaptopurine. The variants of this enzyme explain the variation in the side effects of these drugs.

B) Variability in Transport Proteins:**1- P-glycoprotein:**

- It is a plasma membrane efflux pump that actively transports many compounds out of the interior of several cell types. There is a considerable inter-individual variability in human P-gp expression.
- For example: on the apical (luminal) surface of epithelial cells such as: intestinal cells (pumps drugs to the lumen against concentration gradient which decreases drug oral absorption), renal proximal tubular cells, and brain capillary endothelial cells of the blood brain barrier (that decrease drugs crossing the blood brain barrier).

2- Multi-Specific Organic Anion Transporter:

Its over-expression is responsible for the majority of non-Pgp mediated multi-drug resistance.

Gene-mutations of these transporters cause different effects of drugs e.g.,

- Serotonin transporters in Alzheimer's disease,
- Dopamine transporters in Parkinson's disease.

III) Pharmacodynamic Variability:

- It is mainly due to variants in the cell-surface receptors or the intracellular signaling pathways.
- Examples:
 - **Malignant hyperthermia** is due to polymorphism in the skeletal muscle calcium release channel at ryanodine receptor gene.
 - **Opioid receptor polymorphism (μ receptors)** explains a decreased affinity for morphine or increased risk of addiction in some patients.
 - **Adrenergic receptor polymorphism** explains the different responses to asthma, hypertension, and congestive heart failure therapy.
 - **Polymorphism of K⁺ voltage-gated channel** is the cause of the long QT syndrome that occurs with some drugs as antihistaminics, antiarrhythmics, or antiemetics.

Important Pharmacogenetic Disorders in Clinical Anesthesia Practice:

- Malignant hyperthermia.
- Porphyria.
- Mucopolysaccharidosis (autosomal recessive).
- Osteogenesis imperfecta (autosomal dominant).
- Neurofibromatosis (Von Recklinghausen's disease).
- Familial dys-autonomia.
- Glucose 6-phosphate dehydrogenase deficiency (G6PD) deficiency.
- Succinylcholine apnea.
- Glycogen storage diseases.
- Marfan syndrome.

DRUG CHIRALITY (ISOMERISM) & ANESTHESIA

Chirality: is the spatial arrangement of atoms; non-superimposable on its mirror image.

Types of Isomers:

I) Constitutional Isomers (Structural Isomers):

- They are isomers whose atoms have a **different connectivity** i.e., they have the same molecular formula, but **different structural formula**.

- They usually have different physical and chemical properties.

For example, enflurane and isoflurane; both are $C_3H_2F_5OCl$.

II) Stereo-Isomers:

- They are compounds (isomers) which have the same constituent atoms and connectivity, but differ in the three-dimensional spatial arrangement of their constituent atoms and may be divided into two groups:

a) Enantiomers (Optical Stereo-Isomers):

- They are stereo-isomers which are non-superimposable mirror images of one another and are pairs of compounds related as an object to its mirror image, **in the same way that an individual's left and right hands** are related. Such molecules are said to be chiral, from the Greek *chiro* meaning handed. A pair of enantiomers has identical physicochemical properties as solubility, melting/boiling point, and ionization....etc. They differ in some pharmacokinetic and pharmacodynamic properties.

- Enantiomers are of two types; **dextrorotatory** and **levorotatory** see later.....

b) Diastereo-Isomers:

- They are stereo-isomers which are not mirror image related (i.e., not enantiomers).

- They are either - Cis-isomers.

or - Trans-isomers.

For example: atracurium and cis-atracurium.

Methods of Classification:

a- The D/L Notation:

It uses standard reference compounds either - The carbohydrate D-glyceraldehyde.

or - The amino acid L-serine.

A particular stereo-isomer being designated as a member of either the D- or L- series and the racemic as D-, L-.

This system is restricted in use for the designation of stereo-isomers of carbohydrates and amino acids.

b- Sequence Rule System:

The substituent atoms bonded to the center of chirality are placed in an order of priority based upon their atomic number, the higher the atomic number the greater the priority. The molecule is then '**viewed**' from the side opposite the group of the lowest priority and if the three remaining **highest to lowest priorities** are in a **clockwise direction** (to the right), the stereo-isomer is assigned the **Rectus** configuration with the prefix **R-**, and if **anticlockwise** (to the left), it is assigned the **Sinister** configuration with the prefix **S-**.

c- Enantiomers are of Two Types:

- **Dextrorotatory:** enantiomers which rotate light to the right, indicated by either a **(+)-sign** or lower case italicized **d-** before their name, or alternatively the prefix '**dex**' or '**dextro**' to the drug name.

- **Levorotatory:** enantiomers which rotate light to the left, indicated by either a **(-)-sign** or lower case italicized **l-** before their name, or alternatively the prefix '**lev**' or '**levo**' to the drug name.

A **racemic mixture:** an **equal parts mixture** of enantiomers being indicated by **(±)-** or **d, l-** before the name, or alternatively the prefix '**rac**' to the drug name.

Drug Chirality and Anesthetic Agents:

Inhalational Anesthetics:

Halothane, isoflurane, enflurane and desflurane are chiral compounds while **sevoflurane is achiral**.

• Halothane:

(+)-R-enantiomer is more potent than (-)-S-halothane in some genetic mutants.

(+)-R-enantiomer is more hepatotoxic than either S- or racemic halothane.

• Isoflurane:

(+)-S-isoflurane is more potent than the (-)-R-enantiomer in increasing sleeping time.

- **Enflurane:**

R-enantiomer is more hepatotoxic than S-enflurane.

Intravenous Anesthetics:

- **Thiopental:**

The S-enantiomer is more potent and has less therapeutic index than the R-thiopental

- **Etomidate:**

It is used as a single stereo-isomer: the R-enantiomer which is 15 folds more potent than the S-etomidate. The later is devoid of hypnotic activity.

- **Ketamine:**

The S-enantiomer is more potent i.e., producing more effective anesthesia, less emergence reactions and agitated behavior than either racemic or R-ketamine. Doses of S-ketamine should be decreased about 70% than racemic ketamine.

It is used in the market as racemate, except recently in Germany, it is marketed as the single S-enantiomer due to its advantages. The re-introduction of a single enantiomer for a number of agents initially or currently; marketed as racemates, is called **chiral switch process**.

Local Anesthetics:

- **Bupivacaine:**

S-(l) enantiomer shows a vasoconstrictor effect and consequently a longer duration of action.

R-(d) enantiomer is more cardiotoxic (more severe dysrhythmia, hypotension up to cardiac arrest) than S-(l) enantiomer because the former is more potent in blocking the cardiac sodium and potassium channels.

- **Prilocaine:**

R-enantiomer is associated with more production of met-hemoglobin than either S- or racemic prilocaine.

Summary: • The more potent and more toxic drugs are:

S-isomers	R-isomers
Isoflurane	Halothane
Thiopentone	Enflurane
	Etomidate
	Bupivacaine
	Prilocaine

- S-Ketamine is more potent and safer.

Advantages of Using Single Enantiomers over Racemates:

1. Less complex and more selective pharmacological profile.
2. Potential for an improved therapeutic index.
3. Less complex pharmacokinetic profile.
4. Decreased potential for complex drug interactions.
5. Less complex relationship between plasma concentrations and effect.

DRUGS USED DURING PREGNANCY

Food and drug administration (FDA) classifies drugs into 5 categories (A, B, C, D, and X) according to the level of risk the drug poses to the fetus if the drug is given to the mother during pregnancy.

Category Description:

Category	Animal Controlled Studies	Human (Women) Controlled Studies
A	Safe	Safe (fail to demonstrate a risk to the fetus in the first trimester and later trimesters) e.g., water.
B Two possibilities	Safe	No controlled studies in women are available.
	Adverse effects (other than a decrease in fertility)	Safe (no risk demonstrated in the first and later trimesters).
C is either	Adverse effects	No controlled studies are available.
	No controlled studies are available.	No controlled studies are available. Drugs should be given only if the potential benefits outweigh the potential risk to the fetus.
D	Adverse effects (such as teratogenicity or embryo-cidal effects)	There is a positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life- or limb-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective) e.g., diazepam.
X	Fetal abnormalities (such as teratogenicity or embryo-cidal effects)	There are fetal abnormalities in controlled studies or there is an evidence of fetal risk from prior human experience The risk of the use of the drug in pregnant women clearly outweighs any possible benefits. The drug is contraindicated in women who are or may get pregnant e.g., thalidomide.

Drugs Categories

Category	Anesthetic Drugs	Other Drugs
A category	No anesthetic drugs in this category	Ferrous sulfate, levo-thyroxin, Magnesium sulfate, Vitamin B1, and Vitamin B6.
B category	<ul style="list-style-type: none"> • Induction agents: Methohexital and propofol • Inhalational agents: enflurane, isoflurane, desflurane, and sevoflurane. 	Amoxicillin, Cefaclor, Cefoperazone, Cephalexin, Ceftriaxone, Cimetidine, Clindamycin, Erythromycin, Famotidine, Indomethacin, Isosorbide, Lactulose, Methyldopa, Metronidazole, Nitrofurantoin, Prednisone, Sucralfate, and Spironolactone.
	<ul style="list-style-type: none"> • Local anesthetics: lidocaine and ropivacaine. • Narcotics: fentanyl and demerol. 	
C category	<ul style="list-style-type: none"> • Induction agents: thiopental, ketamine, and etomidate. • Inhalational agents: halothane. • Local anesthetics: 2-chloroprocaine and bupivacaine. • Narcotics: morphine and sufentanil. 	Acetaminophen, Acyclovir, Adenosine, Allopurinol, Aminophylline, Alcohol, Amphetamine, Anti-hemophilic factors, Atropine sulfate, Calcium injection, Chloroquine, Chlorpheniramine, Chlorpromazine, Ciprofloxacin, Clofazimine, Clonidine, Clotrimazole, Dapsone, Dexamethasone, Digoxin, Diltiazem, Ethionamide, Furosemide, Gentamycin, Guafensin, Haloperidol, Heparin, Hydralazine, Interferon, Isoniazid, Ketoconazole, Neostigmine, Nifedipine, Norfloxacin, Prazosin, Rifampicin, Streptokinase, Vitamin K, and Zidovudine.

D category	No anesthetic drugs in this category	Alprazolam, Amikacin, Amiodarone, Amitriptyline, Aspirin, Atenolol, Captopril, Colchicine, Doxycycline, Enalapril, Eosinophil, Kanamycin, Lisinopril, Lithium, Lorazepam, Neomycin, Oxazepam, Ramipril, Tamoxifen, and Valproic acid.
X category	No anesthetic drugs in this category	Ergotamine, Phenobarbital, Clomiphene, Danazol, Estradiol, Levo-norgestrel, Oxytocin, Quinine sulphate, Stanozolol, Vitamin A, and Warfarin sodium.

N.B.: Nitrous oxide is not classified in any of these categories.

Antimicrobials and Pregnancy

A) Drugs may be Used During Pregnancy

Drug	Comments
<ul style="list-style-type: none"> • Penicillin • Ampicillin • Amoxicillin 	<ul style="list-style-type: none"> • There is a possibility of sensitization of the fetus. • All the common β-lactams may be described as safe.
<ul style="list-style-type: none"> • Amoxicillin and Clavulanic acid • Ticarcillin • Carbenicillin • Piperacillin • Cloxacillin • Cephalexin and other injectable cephalosporins 	<ul style="list-style-type: none"> • Little information is available, so they are best avoided till more experience is reported.
<ul style="list-style-type: none"> • Sulphonamides 	<ul style="list-style-type: none"> • Safe in the first trimester. • They should be avoided within 2 days of the delivery. • The risk is more with highly protein bound agents as sulphafurazole.
<ul style="list-style-type: none"> • Trimethoprim 	<ul style="list-style-type: none"> • Theoretical risk of megaloblastic anemia.
<ul style="list-style-type: none"> • Cotrimoxazole 	<ul style="list-style-type: none"> • Kernicterus may occur in the fetus.
<ul style="list-style-type: none"> • Nitrofurantoin 	<ul style="list-style-type: none"> • It is risky in glucose-6-phosphate dehydrogenase deficiency.

B) Drugs Used Cautiously During Pregnancy

<ul style="list-style-type: none"> • Gentamycin • Amikacin • Tobramycin • Netilmicin 	<ul style="list-style-type: none"> • Theoretical risk of ototoxicity in the fetus. • They are used only if they are highly indicated
<ul style="list-style-type: none"> • Nalidixic acid 	<ul style="list-style-type: none"> • There are conflicting data.
<ul style="list-style-type: none"> • Vancomycin 	<ul style="list-style-type: none"> • Safety data are not available for humans.
<ul style="list-style-type: none"> • Metronidazole 	<ul style="list-style-type: none"> • Theoretical risk of teratogenicity in the fetus.

C) Drugs should be avoided During Pregnancy:

<ul style="list-style-type: none"> • Tetracycline 	<ul style="list-style-type: none"> • Discoloration and dysplasia of teeth and bones, and cataract in the fetus. • Hepatotoxicity in the mother.
<ul style="list-style-type: none"> • Streptomycin 	<ul style="list-style-type: none"> • Ototoxicity.
<ul style="list-style-type: none"> • Ciprofloxacin • Ofloxacin • Pefloxacin 	<ul style="list-style-type: none"> • Little experience during pregnancy.
<ul style="list-style-type: none"> • Erythromycin 	<ul style="list-style-type: none"> • Maternal hepato-toxicity in late pregnancy.
<ul style="list-style-type: none"> • Clarithromycin • Azithromycin • Clindamycin • Lincomycin 	<ul style="list-style-type: none"> • Maternal pseudo-membranous colitis
<ul style="list-style-type: none"> • Chloramphenicol 	<ul style="list-style-type: none"> • Grey baby syndrome in the fetus. • Maternal blood dyscrasias.

To Remember Doses of the Anesthetic Drugs:

Most of anesthetic drugs are presented from the manufacturing companies as one ampoule or vial for one dose for a 70 kg adult, so if you divide the content of the ampoule on 100, this will give you usually the minimal dose of drug/kg. **For example:**

Drug	Presentation	Minimal Dose /kg
Thiopentone	500 mg vial	5 mg/kg
Propofol	200 mg ampoule	2 mg/kg
Atropine	1 mg ampoule	0.01 mg/kg
Suxamethonium	100 mg ampoule	1 mg/kg
Fentanyl	100 µg ampoule	1 µg/kg
Morphine	10 mg ampoule 20 mg ampoule	0.1 mg/kg by i.v. routes 0.2 mg/kg by i.m. routes
Meperidine	50 mg ampoule 100 mg ampoule	0.5 mg/kg by i.v. routes 1 mg/kg by i.m. routes
Ketamine	500 mg multiuse vial in 10 mL (50 mg/mL)	5 mg/kg by i.m. or oral routes 1 mg/kg for i.v. routes as it is multiuse vial.
Atracurium	50 mg ampoule 25 mg ampoule	0.5 mg/kg for intubating doses 0.25 mg/kg for loading doses
Pancuronium	4 mg ampoule	0.04 mg/kg for loading doses 2 ampoules are needed for the intubating dose 0.08 mg/kg
Prostigmine (for the reversal of muscle relaxants)	5 mL multiuse vial (2.5 mg/mL) 1-2 mL are used in the reverse (2.5-5 mg)	25 µg/kg (1 mL) to 50 µg/kg (2 mL)

This is only just my observation on drug presentation.

All doses in this book are only a guide, but accurate doses should be revised with the pharmacopoeias. The physician must give the suitable dose of each drug for each patient; for example, in opioids, the dose must be increased if severe pain is present and must be decreased in elderly or in patients with liver diseases.

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Web Sites:

- <http://www.biomedcentral.com/bmcpharmacol/>
- <http://www.clinicalpharmacology.com/>

BASIC PHYSICS FOR ANESTHESIA & INTENSIVE CARE

5

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Part 1: BASIC UNITS AND DEFINITIONS

Initially, measurements were related to commonly available objects; thus in **early Egyptian times** length was related to the width of the finger (the digit) or to the distance from the elbow to the fingertips (the cubit).

Units of Measurement

Two main systems of measurement were used:

- **The Imperial or British system:** based on the Foot (length), Pound (mass), Second (time) (FPS). Disadvantages: the interrelationship between its units is not systematic e.g., one mile = 1760 yards while one foot = $1/3$ yard.

- **The Metric or French system:** based on Centimeter (length), Gram (mass), and Second (time) (CGS), that were later replaced by Meter, Kilogram, and Second (MKS).

The French system was first developed in France at the end of the 18th century. In 1960, further refinement and extension of this system occurred to be the **Système Internationale d'Unités (SIU)**. This occurred in an international conference on weights and measures held at Sèvres; a suburb of Paris.

The replacement of the imperial by the metric system has proceeded in different countries. All units relevant to medical practice have become metric, but the change to SI has been patchy and has not yet been established in many countries.

Système Internationale d'Unités (SIU)

It consists of seven base units and many derived units.

A) The Seven Base SI Units:

Physical Quantity	Unit	
	Name	Symbol
Length	Meter	M
Mass	Kilogram	Kg
Time	Second	S
Electric current	Ampère	A
Thermodynamic temperature	Kelvin	K
Amount of substance	Mole	Mol
Luminous intensity	Candela	Cd

Definitions of the Seven Base Units:

The meter (m) (the unit of length): is the length equal to a specific number of wavelengths of the orange light of specified emission, in a vacuum, from the krypton-86 atom.

N.B.: • Initially the meter, was supposed to be a distance equal to $1/10\,000\,000$ of the distance along the Earth's surface between the pole and equator.

- Later on, the standard meter was the length of a bar made of platinum and iridium and kept at Sèvres.

- In 1960, as the need for greater accuracy has become apparent, the International Bureau of Weights and Measures at Sèvres turned towards standards present in natural phenomena, as these can be measured by scientists anywhere in the world (length of wavelengths emitted from krypton-86).

The kilogram (kg) (the unit of mass): is equal to the mass of the international prototype kilogram, a platinum-iridium cylinder preserved at the International Bureau of Weights and Measures at Sèvres, Paris. The platinum-iridium alloy is used because it has a thermal coefficient of expansion close to zero i.e., its mass does not change by temperature.

The second (s) (the unit of time): is the duration of a specific number of periods of the radiation (frequencies) of the structure transitions in the atoms of caesium-133.

The ampère (A) (the unit of electric current): is the amount of electric current which when flows down each of two parallel conductors of infinite length and negligible circular cross-sectional area and placed one meter apart in a vacuum, would generate between these conductors a force equal to 2×10^{-7} newton per meter of length.

N.B.: It represents a flow of 6.24×10^{18} electrons per second past some point.

The kelvin (K) (the unit of thermodynamic temperature): is $1/273.16$ of the thermodynamic temperature of the triple point of water (the point at which solid, liquid, and gaseous phases are in equilibrium).

The mole (m) (the unit of the amount of substance): is the amount of substance of a system which contains as many elementary entities (atoms, molecules, ions, electrons) as there are atoms in 0.012 kg of carbon 12.

N.B.: The mole represents the gram molecular weight of the substance.

The candela (cd) (the unit of luminous intensity): is defined in terms of the brightness of light (looked at perpendicularly) of a small area of molten platinum at a given temperature and pressure.

B) The Derived Units:

All the derived units are derived from the seven base units. They include:

Physical Quantity	Unit		Expression
	Name	Symbol	
Frequency	Hertz	Hz	1 Hz = 1 cycle/s = s ⁻¹
Force	Newton	N	1 N = m.kg.s ⁻²
Pressure, stress	Pascal	Pa	1 Pa = N.m ⁻²
Energy, work, quantity of heat	Joule	J	1 J = N.m
Power	Watt	W	1 W = J.s ⁻¹
Electric charge, quantity of electricity	Coulomb	C	1 C = s.A.
Electric tension, Electric potential,	Volt	V	1 V = W.A ⁻¹
Electric resistance	Ohm	Ω	1 Ω = V.A ⁻¹
Electric conductance	Siemens	S	1 S = A.V ⁻¹
Electric capacitance	Farad	F	1 F = C.V ⁻¹
Temperature	Degree Celsius	°C	1 °C = K - 273.15

N.B.: 1 per 10 (1/10) can also be expressed as 0.1 which in turn can be represented as 10 to the minus power of 1 (10⁻¹) e.g., N.m⁻² = N/m².

Other Derived Physical Quantities can be derived from the base units, but have not yet been given special names. They include:

Physical Quantity	SI Unit	Symbol for Unit
Area	square meter	m ²
Volume	cubic meter	m ³
Density	Kilogram per cubic meter	kg. m ⁻³
Velocity	Velocity	m.s ⁻¹
Acceleration	meter per second squared	m.s ⁻²
Kinematic viscosity	square meter per second	m ² .s ⁻¹
Dynamic viscosity	newton second per square meter i.e., pascal second	N.s.m ⁻² or Pa.s
Surface tension	newton per meter	N.m ⁻¹

Decimal Multiples and Submultiples (Fractions)

- These are prefixes which are normally attached to the appropriate unit as in millisecond (ms or s x 10⁻³).
- Compound prefixes such as millimicrometer are not permitted.
- Some prefixes use the same letter e.g., 'm' is used for both milli and meter. To clarify the meaning it is necessary to observe the unit symbol preceded by the prefix without space or punctuation. Thus ms indicates millisecond and mm millimeter. To denote the product of two symbols, the symbols are separated by a space or by a central point. Thus meter x second is m s or m.s whilst meter per second is m s⁻¹ or m.s⁻¹.

Prefixes for SI units are:

Multiples			Submultiples (Fractions)		
Prefix	Symbol	Factor	Prefix	Symbol	Factor
Deca	Da	10 ¹	Deci	D	10 ⁻¹
Hectar	H	10 ²	Centi	C	10 ⁻²
Kilo	K	10 ³	Milli	M	10 ⁻³
Mega	M	10 ⁶	Micro	μ	10 ⁻⁶
Giga	G	10 ⁹	Nano	N	10 ⁻⁹
Tera	T	10 ¹²	Pico	P	10 ⁻¹²
Peta	P	10 ¹⁵	Femto	F	10 ⁻¹⁵
Exa	E	10 ¹⁸	Atto	A	10 ⁻¹⁸

Special Authorized Names and Symbols

These units can be defined in terms of the base units, but there do not have decimal multiples or submultiples. They include:

Physical Quantity	Unit		
	Name	Symbol	Value
Volume	Liter	L or l	1 L = 1 dm ³ = 10 ⁻³ m ³
Mass	metric ton	T	1 t = 1 Mg = 10 ³ kg
Pressure	Bar	Bar	1 bar = 10 ⁵ Pa

Non-SI Units Temporarily Retained

These are non-SI units, but are still in common use in medical practice. They include:

- The minute (min), hour (h), and day (d) as units of time.
- The dyne (dyn) as a unit of force.
- The bar and psi as units of pressure of compressed gases.
- The mmHg (millimeter of mercury) (torr) as a unit of blood pressure.
- The cm H₂O as a unit of central venous pressure (CVP).
- The calorie (cal) as a unit of heat energy.

In humans, the calorie is a very minute amount; therefore, kilocalorie is used instead. Kilocalorie is written as follows; kcal = big calorie = Calorie "with a capital C letter" = 1000 calories.

- The poise (P) for dynamic viscosity.
- The stokes (St) for kinematic viscosity.

Advantages of the Systeme Internationale d'Unités (SIU)

- 1- **Standardization:** the use of one standard unit for each physical quantity.
- 2- **Decimalization:** decimal multiples and submultiples of any unit can be derived by adding one standard prefix to the unit.
- 3- **Simplification:** the decimal basis of SI system makes calculations very simple.

Basic Definitions (see above for the SI units)

Length (l): is defined as the distance between two points.

Velocity (v): is defined as the distance travelled per unit time: $\text{velocity (v)} = \frac{\text{distance}}{\text{time}}$

Acceleration (a): is defined as the rate of change of velocity: $\text{acceleration (a)} = \frac{\text{velocity}}{\text{time}}$

Momentum: is defined as mass multiplied by velocity: $\text{momentum} = \text{mass} \times \text{velocity}$

Inertia: is defined as the resistance to change of velocity of moving object.

Newton's Laws of Motion: They are 3 laws:

- **First law:** A body remains at rest or continues to move with a uniform velocity unless an external force acts on it.
- **Second law:** The rate of change of momentum is proportional to the force producing the change, and the change takes place in the direction of the force.
- **Third law:** To every action, there is an equal and opposite reaction.

Mass (m): is defined as the amount of matter in a body.

Force (F): is defined as the action required to change or tend to change the state of rest or motion of an object i.e., give a mass acceleration): $\text{force} = \text{mass} \times \text{acceleration}$

The SI unit of force is the newton (N). **One newton** is the force required to give a mass of 1 kg an acceleration of 1 m.s⁻².

Weight (W): is the force of the Earth's attraction for a body or the force exerted by gravity on a mass:

$$\text{Weight} = \text{mass} \times \text{gravity} = \text{mass} \times 9.81 \text{ m.s}^{-2}.$$

- When a body falls freely under the influence of gravity, it accelerates at a rate of 9.81 m.s⁻². That means the force of gravity on a mass of 1 kg equals 9.81 N. This force is known as 1 kg weight, and so 1 newton is equivalent to 1/9.81 kg weight i.e., 102 gram weight.
- The mass of a body does not depend on its location, but the weight does. The mass of the body remains constant whether on Earth, on Moon, or any other place. Therefore, when a body is located in the space outside the Earth's gravity or at the center of Earth, it loses its weight, but not its mass. The body becomes weightless because the Earth's gravity is zero: $\text{Weight} = \text{mass} \times \text{gravity}$
 $= \text{mass} \times \text{zero} = \text{zero}$

Density (ρ): is the mass per unit volume: $\text{density} = \text{mass} / \text{volume}$

Pressure (P): is defined as force per unit area: $\text{pressure} = \frac{\text{force}}{\text{area}}$

Work (U): is performed when a force moves an object: $\text{work} = \text{force} \times \text{distance}$

The SI unit of the work is joule (J). 1 joule = 1 N.m.

When the work is done, the force gives energy to the body. Therefore, the mechanical work is a form of energy.

Energy (U): is the capacity for doing work: $\text{energy} = \text{force} \times \text{distance}$.

Thus it has the same units as those of work.

Forms (types) of energy include:

1. Kinetic (mechanical) energy: the energy possessed by the body due to its motion.
 2. Potential (position) energy: the energy possessed by the body due to its position.
 3. Heat energy: the energy obtained from hot bodies.
 4. Chemical energy: the energy obtained from food and fuel.
 5. Electric energy: the energy obtained from electric current.
 6. Nuclear energy: the energy stored in the nucleus of an atom.
- All forms of energy are interchangeable. The device that converts one form of energy into another is called a transducer. Law of conservation of energy: states that the total energy of a body or a system remains constant.
 - Total energy = potential energy + kinetic energy = constant.
 - The force of gravity on an apple which has a mass of 102 grams is 1 newton, so if the apple is raised 1 meter vertically against the force of gravity, 1 joule of work is performed. The total energy must remain constant and, in this case, the kinetic (mechanical) energy expended in raising the apple is converted into potential energy represented by the additional height of the apple.
 - Force in the body normally arises from muscular contraction; the shortening of the muscle multiplied by the mean force exerted is the mechanical work performed.

Power (P): is the rate of doing work: $\text{power} = \text{work per unit time}$.

The SI unit of the power is the watt (W). 1 watt = 1 J.s⁻¹.

The old unit of power is the horsepower (one horsepower = 746 W).

Frequency: is the number of cycles per second

The SI unit is the hertz (Hz) e.g., patient's pulse 120/ min = 2/ sec = 2 Hz.

Part 2: EXPONENTIAL CURVES

Introduction

A **graph** is a visual expression of the relationship between two variables. A graph has two axes:

- **The horizontal or the X-axis (abscissa):** on which the independent variable is plotted.
- **The vertical or the Y-axis (ordinate):** on which the dependent variable is plotted.

The Relationship between the Variables may be:

a- Linear Relationship:

It is represented by a **line** (figure 5-1). It occurs when the **rate of change** between the two variables occurs by **equal amounts** e.g., - Laminar flow in a uniform tube.

- Expansion of mercury in a thermometer.

b- Nonlinear Relationship:

Exponential Process or Function: a special form of nonlinear change often encountered in medicine.

It is represented by a **curve**. It occurs when the rate of change between the two variables occurs by **constant proportions**.

For example, during the emptying of the bath, initially, emptying of the bath is faster because of the high column of water and the high pressure above the plug hole, but as the column of the water gets less, the rate at which the bath empties becomes slower. Therefore, a plot of volume against time is a curve steep initially and gradually getting less steep as the emptying slows (figure 5-2).

The rate at which the bath empties (\dot{Q}) is proportional to the volume or the quantity of the water (Q) in it, which makes the process exponential i.e., $\dot{Q} \propto Q$. Therefore, in an exponential process, the rate of change of a quantity (\dot{Q}) at any time is proportional to the quantity at that time.

N.B.: a small dot is added to the letter Q as in \dot{Q} to differentiate between the quantity per unit time i.e., the rate and the quantity as a volume.

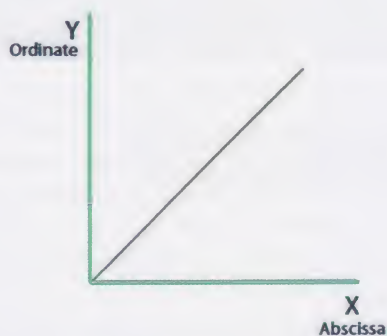


Figure 5-1: Linear relationship



Figure 5-2: The bath and the tap

Types of Exponential Curves:

1- The Negative Exponential Curve:

It is also called the **washout or decay curve** (figure 5-3). For example:

- Deflation of the lung.
- Elimination of inhalational anesthetic agents.
- Decay of radio-active isotope.
- Nitrogen washout lung function test.

2- The Positive Exponential Curves:

a- Build-Up Curve:

It is more relevant to anesthesia than other curves. It appears like an inverted negative exponential curve (figure 5-4). For example: - Inflation of the lungs with a constant-pressure ventilator.

- Dose-response curve of drugs.
 - Uptake of inhalational anesthetic agents during induction of anesthesia.
- Actually, uptake of inhalational agents is formed from many exponential curves; lung uptake curve, blood uptake curve, and tissue uptake curve.

b- Run-Away or Break-Away Curve: (figure 5-5)

For example: - Growth of bacteria in presence of unlimited nutrients.

- Multiplication of some cancer cells.

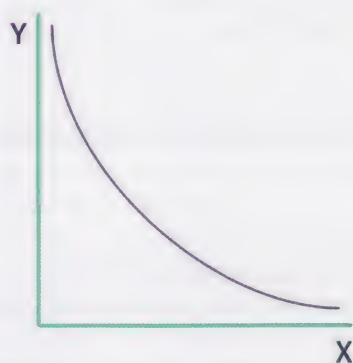


Figure 5-3: Washout curve

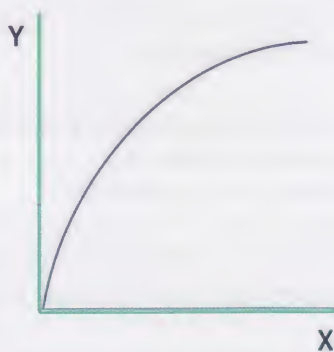


Figure 5-4: Wash-in (build-up) curve

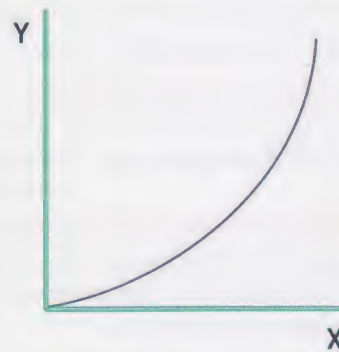


Figure 5-5: Run-away curve

Duration of Exponential Function:

In exponential process, although the quantity decreases (in washout curve), it never actually reaches zero. Consequently, the total length of time taken by the exponential process is infinite and the total time

cannot be used to measure the duration of the exponential process. Therefore, alternative values are used to describe the rate of any exponential process:

The Half-Life ($t_{1/2}$):

It is represented by $t_{1/2}$. It is the time taken for the quantity (Q) to decrease to half its initial value i.e., after one half-life, 50% of the exponential process is completed and 50% remains (figure 5-6).

Uses: The half-life is used to describe:

- **The decay of radioactive isotopes:** If an isotope has a half-life of 1 hour, then after 1 hour the radioactivity is 50% of its initial value, after 2 hours 25%, after 3 hours 12.5%, and so on.
- **The pharmacokinetics of drugs:** 5 x the half-life of the drug is required either to:
 - achieve complete elimination of the drug.
 - or - achieve a steady state plasma concentration with continuous intravenous infusion of the drug.

The Time Constant (τ):

It is represented by the Greek letter tau (τ). It is the time taken for the quantity (Q) to decrease to 37% of its initial value i.e., after one time constant, 63% of the exponential process is completed and 37% remains (figure 5-6). Consequently, the time constant is longer than the half-life.

The figure 37% results from the mathematical solution of equations used to analyze exponential processes by using the **natural logarithm** (which is the logarithm to the base e 'log e'. The letter 'e' denotes exponential). The mathematical value of the log or exponential (e) is 2.718. It is used to calculate the time constant of the exponential process:

$$\text{The time constant} = \frac{1}{e} = \frac{1}{2.718} = 37\%$$

Uses: The constant time is used to:

- **Describe the expiration:** If the expiratory time constant is 0.3 second, then the values of the tidal volume (V_t) that is expired and that is remaining in the lungs are as follows:
 - After 0.3 s (1 τ), 63% of the V_t is expired and 37% remains in the lungs.
 - After 0.6 s (2 τ), 86.5% of the V_t is expired and 13.5% remains in the lungs.
 - After 0.9 s (3 τ), 95% of the V_t is expired and only 5% remains in the lungs.

Thus, expiration is 95% complete after 3 time constants.

The expiratory time constant can be calculated if the compliance C and resistance R of the lung are known. The expiratory time constant $\tau = C \times R$

$$= 0.5 \text{ L/kPa} \times 0.6 \text{ kPa/L} \\ = 0.3 \text{ second}$$

- **Measure the blood flow to organs by radioactive isotopes:**

In a washout curve, the time constant (τ) = $\frac{\text{Volume undergoing washout}}{\text{Flow of perfusing fluid}}$

A radioactive isotope with a known volume is injected into the organ and the rate at which it is washed out by the blood is measured by a scintillation counter. From this, the time constant is measured. Therefore, the blood flow to this organ can be calculated.

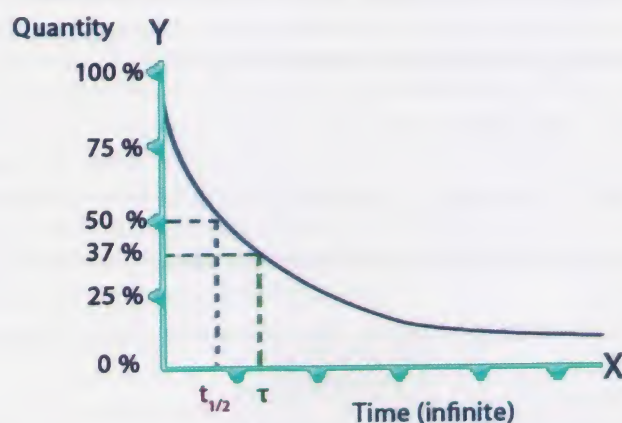


Figure 5-6: The half-life and the time constant

Part 3: STRUCTURE AND PHYSICAL PROPERTIES OF MATTER

Definitions

Matter: is composed of molecules and atoms.

A molecule: is a group of atoms.

An atom: is the smallest particle into which an element can be subdivided (figure 5-7).

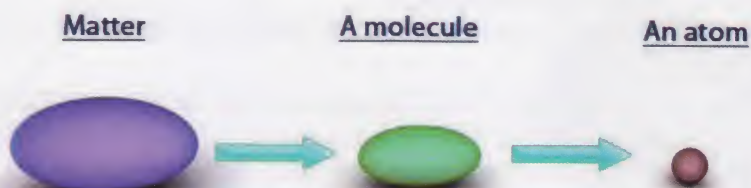


Figure 5-7: The matter, a molecule, and an atom

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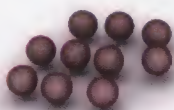
An element: - is composed of similar atoms.

- has distinctive physical and chemical properties.
- e.g., hydrogen, oxygen, nitrogen, helium....etc.

A compound: - is composed of two or more elements chemically united to form a substance.

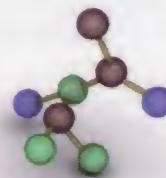
- has different physical and chemical properties than the individual elements forming it.
- e.g., water (H_2O), carbon dioxide (CO_2)...etc (figure 5-8).

An element



Similar atoms

A compound



Two or more elements

Figure 5-8: An element (left) and a compound (right)

Atom:

There are 103 atoms which differ in their atomic number and weight.

Atomic number Atom Atomic weight e.g., ${}_8\text{O}^{16}$

Atomic weight: is the weight of an atom in relation to oxygen atom (which is 16) or hydrogen atom (which is one).

Atomic number: is the number of electrons or protons of the atom.

Molecular Weight (MW):

It is the weight of one molecule in Dalton (Da) i.e., the summation of the weights of atoms e.g.,

- The MW of H_2O = 2 H atoms \times 1 + 1 O atom \times 16 = 18 Da
- The MW of CO_2 = 1 C atom \times 12 + 2 O atoms \times 16 = 44 Da
- The MW of N_2O = 2 N atoms \times 14 + 1 O atom \times 16 = 44 Da
- The MW of glucose ($\text{C}_6\text{H}_{12}\text{O}_6$) = 6 C atoms \times 12 + 12 H atoms \times 1 + 6 O atoms \times 16 = 180 Da
- The MW of NaCl = 1 Na atom \times 23 + 1 Cl atom \times 35.5 = 58.5 Da.

Gram-Molecular Weight:

It is the molecular weight in grams. It represents one mole e.g.,

- The gram MW of H_2O = 18 gram i.e., 1 mole.
- The gram MW of CO_2 = 44 gram i.e., one mole.
- The gram MW of N_2O = 44 gram i.e., one mole.
- The gram MW of glucose ($\text{C}_6\text{H}_{12}\text{O}_6$) = 180 gram i.e., one mole
- The gram MW of NaCl = 58.5 grams i.e., one mole.

Mole:

The mole (mol) is the SI unit for expressing the amount of a substance.

One mole of a substance represents 6.02×10^{23} molecules (Avogadro's number) i.e., moles of all substances contain the same number of molecules.

In the human being, the mole is a very large amount; therefore, the millimole (mmol) is used instead which is 1/1000 of a mole.

Molarity:

It is the SI unit of the concentration of a solution that expresses the **number of moles** of solute per **liter** of solution (mol/L) (figure 5-9).

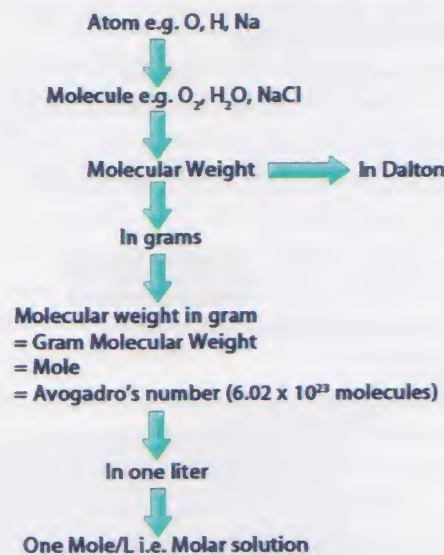


Figure 5-9: The molecular weight

Physical States of Matter

Matter can exist in three physical states:

- **Solids:** their molecules cannot move freely, but can oscillate. The molecules are close to each other and cannot change their positions. Therefore, solid objects have fixed volumes and fixed shapes.
- **Liquids:** their molecules can move freely. The molecules can change their positions. Therefore, liquids have a fixed volume, but no fixed shape because they take the shape of any container.
- **Gases:** their molecules can move more freely than those in liquids. The molecules can change their positions. Therefore, gases have no fixed volume and no fixed shape because they expand to occupy the total space of a container.

N.B.: Both liquids and gases are called **fluids** because their molecules can flow freely.

Heating a liquid increases the kinetic energy of its molecules allowing them to escape from the liquid phase into the gaseous phase forming a **vapor**.

Density

Definition: Density (ρ rho) is defined as the mass per unit volume of a substance.

The SI Unit of Density is kg/m^3 . The unit g/cm^3 is also used.

N.B.: Density is temperature dependent e.g., - density of water is 1 g/cm^3 at 4°C .

and - density of mercury is 13.6 g/cm^3 at 20°C .

Specific Gravity (SG) or Relative Density:

- Specific gravity of a gas is its density relative to that of air which is taken as 1.
- Specific gravity of a liquid is its density relative to that of water which is taken as 1.

Clinical Applications: Baricity

It is the specific gravity of a local anesthetic solution relative to that of the cerebrospinal fluid (CSF) at 37 °C. The specific gravity of CSF at 37 °C is 1.003- 1.009 (1.006).

Local anesthetic solutions are manufactured with different specific gravities as follows:

- **Isobaric local anesthetic solutions** have the **same SG** as that of CSF. If an isobaric local anesthetic solution is injected in the CSF within the subarachnoid space during spinal anesthesia, it tends to remain in its place and block the nerves around the site of injection. It is prepared by **mixing** the local anesthetic solution **with isotonic 0.9% saline**, or by dissolving the local anesthetic drug in the **patient's CSF** just before subarachnoid injection.
- **Hypobaric local anesthetic solutions** have **lower SG** than that of the CSF. If a hypobaric local anesthetic solution is injected in the CSF within the subarachnoid space during spinal anesthesia, it tends to migrate to higher levels and block the nerves above the site of injection. It is used in ano-rectal surgeries in which spinal anesthesia is done in the prone position or in hip surgeries in which spinal anesthesia is done in the lateral position where the diseased side is the upper one. It is prepared by **mixing** the local anesthetic solution **with sterile distilled water**.
- **Hyperbaric local anesthetic solutions** have **higher SG** than that of the CSF. If a hyperbaric local anesthetic solution is injected in the CSF within the subarachnoid space during spinal anesthesia, it tends to migrate to lower levels and block the nerves below the site of injection. It is the most commonly used one e.g., during saddle block. It is prepared by **mixing** the local anesthetic solution with **5-10% dextrose solution**.

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Viscosity

Definition: Viscosity is the resistance of a fluid to flow.

Factors Affecting Viscosity:

- It depends on:
- the intermolecular forces present in the fluid as increased intermolecular forces increase the viscosity.
 - the temperature as cooling increases the viscosity.

Types of Viscosity:

a- Dynamic Viscosity (Absolute Viscosity) (η)

It is the **resistance of a viscous fluid** when it flows through a uniform tube in a **laminar way**. The linear velocity of adjacent layers of fluid is different. It is zero at the periphery and maximum at the center resulting in a **parabolic (curved) flow profile** (figure 5-10).

The SI unit of dynamic viscosity is either: - newton second per square meter (N.s/m^2)
or - pascal second (Pa.s).

N.B.: Poise (P) is another unit of dynamic viscosity.

$$1 \text{ Poise} = 1/10 \text{ N.s/m}^2 \\ = 1 \text{ dyne second/cm}^2$$

Dynamic viscosity of the water is 1 centipoise at 20 °C.



Figure 5-10: Laminar flow

Forces Affecting the Dynamic Viscosity:

1- **Shear stress:** the force applied over a layer having a surface area. It pushes the flow of fluid from a point of higher pressure to another point of low pressure.

$$\text{Shear stress} = \frac{\text{Force (F)}}{\text{Crosssectional area (A)}}$$

2- **Shear strain:** the force needed to cause friction of one layer over the other. It makes the velocity gradient between layers. It acts opposite the shear stress.

$$\text{Shear strain} = \frac{\text{velocity gradient (V)}}{\text{distance between 2 layers (X)}}$$

Shear strain is directly proportionate to the shear stress although both are acting in opposite direction.

Newtonian's Law of Viscous Flow:

The **viscosity** of viscous fluid is **not affected by the flow rate** of this fluid.

This law is only for the **homogenous fluids** under conditions of pure laminar flow and the fluid is called "Newtonian fluid" e.g., plasma.

N.B.: Blood is **not** a "Newtonian fluid" because it contains cells as red blood cells which tend to aggregate at very low flow rates; therefore, it is not homogenous.

→ **Kinematic (Relative) Viscosity:** (η/ρ "n/p")

It is defined as dynamic viscosity/density.

The **onset of turbulent flow** depends on the kinematic viscosity of the fluid. The greater the kinematic viscosity, the greater velocity needed to initiate turbulent flow i.e., less possibility of turbulent flow. For example, as the kinematic viscosity of O₂ is twice that of N₂O; therefore, flow of N₂O becomes turbulent more easily than O₂ i.e., turbulent flow of O₂ occurs at a higher velocity. When a viscous fluid flows through a uniform tube in a turbulent way, it will have a **flat flow profile** (figure 5-11).

The **SI unit** of kinematic viscosity is square meter per second (m²/s).

N.B.: Stokes (ST) is another unit of kinematic viscosity.

$$1 \text{ stokes} = 1 \text{ cm}^2/\text{s}$$



Figure 5-11: Turbulent flow

Blood Viscosity:

• **Increased blood viscosity** reduces blood flow, giving a risk of vascular occlusion, for example:

- increased Hb concentration,
- hypothermia,
- advanced age,
- cigarette smoking,

and - very low flows such as in areas with intermittent circulation because the blood is a non-newtonian fluid.

• **Decreased blood viscosity** increases blood flow and thus improves the peripheral circulation, for example: - treatment with low-molecular weight dextran, and - hemodilution by intravenous fluids.

N.B.: The kinematic viscosity of plasma is 1.5 and that of whole blood is 3.5 (compared with water).

A Viscometer is the device used to measure viscosity.

→ **A typical viscometer:** a sample of blood is placed in a cone-shaped cup which is kept at a set temperature. The cup is rotated or oscillated. A cone-shaped probe within the cup is dragged by the viscosity of the blood and the torque generated is used to provide a measure of the viscosity.

b- **Other recent viscometers:** measure the viscosity by measuring the time taken for a sample of fluid to flow down a vertical tube. The transit time is measured by photocells and the viscosity is then determined.

Surface Tension

Definition:

Surface tension is the force of contraction across a line of a unit length. The line and the force are perpendicular to each other in the plane of the liquid surface.

Molecular Basis:

- Surface tension is the property of all liquids. It occurs at the junction between a liquid and another immiscible phase e.g., liquid/gas interface.
- At the surface of a liquid: (figure 5-12)
 - Some of the forces of attraction between the molecules act in a direction parallel to the surface of the liquid and result in the liquid surface behaving as though a skin is present. This is known as the surface tension. If all the forces between the molecules on either side of an imaginary straight line on the surface of the liquid are summed, the resulting surface tension may be expressed in terms of force per unit length.
 - A molecule at the surface is only attracted by molecules within the liquid, so that it tends to be pulled inwards and its motion is restricted. Therefore, the surface of the liquid is pulled inwards to occupy the least possible area. The attractive force between the liquid molecules at the surface tends to contract the surface of the liquid to the smallest possible area. As the sphere has the smallest surface area of all geometrical figures, the droplets of water and soap bubbles assume a spherical shape when they fall in air.
- At the depth of a liquid: a molecule within the liquid is attracted equally in all directions by other molecules and so, it can move in any direction.
- At the walls of the container: (figure 5-13)

There are also forces between the molecules and the walls of the containing vessel. These forces result in the meniscus; the curvature of the liquid surface at its contact with the wall. Because of the meniscus, when the lower end of a vertical glass capillary tube is immersed in water, the surface tension at the junction of the water and the wall of the tube acts to some extent in a vertical direction and pulls the water up the tube until it is balanced by the force of gravity on the water in the tube that is above the normal liquid level.



Figure 5-12: Surface tension at the surface



Figure 5-13: Surface tension at the wall of container

The SI Unit of Surface Tension:

is Newton/meter (N/m).

Millinewton/meter (mN/m) is more commonly used.

N.B.: Dyne/cm was used before in the CGS system.

The surface tension is **temperature dependent**.

The surface tension of water at 20 °C = 75 mN/m.

The surface tension of blood at 37 °C (in vivo) = 58 mN/m.

Pulmonary Surfactant

Pulmonary surfactant is a lipoprotein mixture containing phospholipids called **Di-palmitoyl lecithin**. The pulmonary surfactant is secreted by **type II alveolar epithelial cells** (type II pneumocytes) forming a layer which is 5 nanometers in thickness. This is in dynamic equilibrium i.e., the amount of surfactant is in a continuous process of formation and degradation.

Action

• Pulmonary surfactant **decreases the surface tension** of the fluid lining the alveoli and the respiratory passages. It forms a monomolecular layer at the interface between the fluid lining the alveoli and the air inside these alveoli. This prevents the development of water-air interface which has about 10 times as much surface tension as does the surfactant-air interface.

• **During deflation of the alveoli**, they decrease in size. Therefore, the surfactant layer is condensed in the alveoli and its concentration increases and that in turn effectively decreases the surface tension and decreases the tendency of the alveolus to collapse (surface tension tends to collapse the alveoli).

• **During inflation of the alveoli**, they increase in size. Therefore the surfactant layer is stretched in the alveoli and its concentration decreases and that in turn effectively increases the surface tension and increases the tendency of the alveolus to collapse preventing its over-stretch.

Therefore, there will be a relatively constant pressure and stability within the alveolus (figure 5-14).

The surface tension in small deflated alveoli is 10-15 mN/m.

The surface tension in large inflated alveoli is 40-50 mN/m.

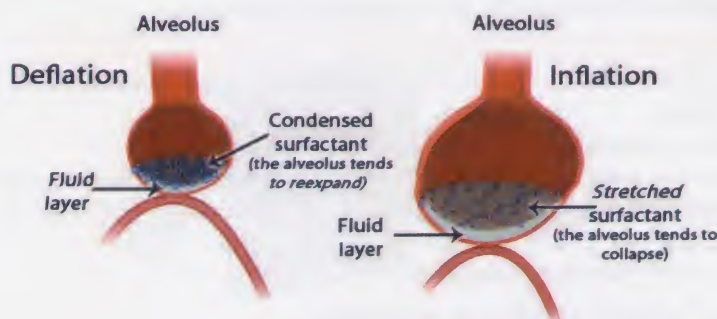


Figure 5-14: Action of surfactant

Law of Laplace

It determines the relationship between the pressure (P), the surface tension (T), and the radius (r).

For a spherical structure: $P = \frac{2T}{r}$

That means; the pressure inside a spherical structure e.g., an alveolus, a bladder, or a heart is directly proportional to double the surface tension and inversely proportional to the radius.

For a cylindrical structure: $P = \frac{T}{r}$

That means; the pressure inside a cylindrical structure e.g., a blood vessel, is directly proportional to the surface tension and inversely proportional to the radius.

Clinical Applications:

If the surface tension is the same in all alveoli, a smaller alveolus will have a higher pressure because its radius is small increasing T/r ratio and a larger alveolus will have a lower pressure because its radius is large decreasing T/r ratio. If the smaller alveolus, with the higher pressure, is in continuity with the larger alveolus, with the lower pressure, the smaller alveolus will empty into the larger one causing collapse of the smaller one.

Normally, this does not occur because the pulmonary surfactant adjusts the surface tension according to the radius. The pulmonary surfactant is concentrated in the smaller alveolus; therefore, its surface tension is decreased and the ratio T/r remains constant and so does the pressure inside the alveolus. The pulmonary surfactant is stretched in the larger alveolus; therefore, its surface tension is increased and the ratio T/r remains constant and the pressure inside the alveolus remains constant as well.

Therefore, the pressure is kept the same in all alveoli. This ensures their stability and prevents their collapse.

Absence or deficiency of pulmonary surfactant causes atelectasis and collapse as in:

- Premature infants with hyaline membrane disease.
- Patients with acute respiratory distress syndrome.
- Patients on cardiopulmonary bypass; because the type II pneumocytes fail to secrete surfactant as the pulmonary circulation is interrupted.

Solubility

Definition

Solubility: is defined as the ability of a substance to dissolve in another substance.

A Solute: is the substance that dissolves in a solution.

A Solvent: is the fluid in which another substance dissolves.

A Solution: is a mixture of two or more substances i.e., a solution = solute + solvent.

A) Solubility of Solids in Liquids:

When a solid (solute) is dissolved in a liquid (solvent), a solution is formed.

The concentration of the solution is expressed in one of the following ways:

1- The Weight of Solute per Unit Volume of Solution:

The most commonly used unit in the body is milligram/deciliter (mg/dL). Also gram/dL is used.

N.B.: dL = 100 mL = %

For example: concentration of blood glucose is 120 mg/dL or mg%.

concentration of hemoglobin is 15 gram/dL or gram%.

2- The Number of Solute Molecules per Unit Volume of Solution:

The most commonly used unit in the body is millimole/Liter (mmol/L) (it is the SI unit of the concentration of a solution).

N.B.: A mole (mol) is the gram molecular weight of a substance.

A mole is too big to be used in the human body; therefore, millimole is the one used.

This method of expressing the concentration is used for the ionized (e.g., Na⁺ and K⁺) and non-ionized solutes (e.g., glucose and urea).

For example: normal serum glucose is 5 mmol/L.

N.B.: Conversion of mg/dL (mg%) to mmol/L:

$$\text{mmol/L} = \frac{\text{mg}\% \times 10}{\text{MW}} = \frac{\text{mg/L}}{\text{MW}}$$

For example:

Blood glucose 90 mg/dL

i.e., 90 mg/100 mL = 900 mg/L

MW of glucose = 1 mole = 180 g.

So, 1 mmol/L → 180 mg/L

X → 900 mg/L

Therefore, 900 mg/L (90 mg/dL) = 900/180
= 5 mmol/L

NaCl 0.9%: i.e., 0.9 g / 100 mL

i.e., 900 mg/100 mL = 9000 mg/L

MW of NaCl = 1 mole = 58.5 g

So, 1 mmol/L → 58.5 mg/L

X → 9000 mg/L

Therefore, 0.9 % = 1 x 9000 / 58.5
= 150 mmol/L

3- The Number of Electrically Charged Particles of Solute per Unit Volume:

The most commonly used unit in the body is milliEquivalent/Liter (mEq/L).

The number of equivalents of an ion in a solution is the number of moles multiplied by its charge (valence) i.e., **Equivalents = n^o of moles x valence.**

or milliEquivalent = n^o of millimoles x valence.

An Equivalent is too big to be used in the human body; therefore, milliEquivalent is the one used.

For monovalent ions e.g., Na⁺ or Cl⁻: Eq/L = mol/L or mEq/L = mmol/L.

For bivalent ions e.g., Ca⁺⁺ or Mg⁺⁺: mEq/L = mmol/L x valence

For example:

- Expressing 2 Ca⁺⁺ mmol/L in mEq/L as follows:

$$2 \text{ Ca}^{++} \text{ mmol/L} \times 2 = 4 \text{ mEq/L}$$

$$\text{i.e., } 2 \text{ mmol Ca}^{++} = 4 \text{ mEq Ca}^{++}.$$

- A one molar solution of MgCl₂ = 2 equivalents of magnesium (2 valence x 1 mole) / liter + 2 equivalents of chloride (1 valence x 2 mole) / liter.

This method of expressing the concentration is used only for the ionized (e.g., Na⁺ and K⁺) solutes.

4- The Number of Osmotically Active Particles of Solute per Unit Volume:

The most commonly used unit in the body is milliosmole/Liter (mOsm/L).

This method of expressing the concentration is used only for the osmotically active particles.

For example, plasma osmolarity is the sum of the osmotically active particles = 290 mOsm/L.

B) Solubility of Gases in Liquids:

Saturated Vapor Pressure (SVP):

At a given temperature, when a liquid is placed in a closed container, an equilibrium is eventually established at the surface, between the vapor of the liquid and the liquid itself. In this equilibrium state, the partial pressure exerted by the vapor is known as the **saturated vapor pressure (SVP)**.

Normally, there is usually at least one gas present above the surface of the liquid in addition to the vapor. At the same time, some of the gas molecules above the liquid will dissolve in the liquid. Therefore, there will be two parts in the closed container (figure 5-15):

- The part above, containing the gas molecules and the vapor (liquid molecules).

- The part below, containing the gas molecules and the liquid molecules themselves.

When the rate of the dissolved gas molecules leaving the liquid equals the rate at which other gas molecules dissolve in the liquid, equilibrium occurs.

Both the liquid and the dissolved gas form a **saturated solution**.

The **partial pressure exerted by the gas molecules** in the solution is called by some authors "**tension**".

This term is also used in physics when it refers to force.

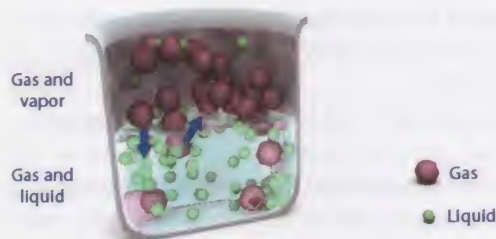


Figure 5-15: Saturated vapor pressure.

Factors Affecting the Solubility of Gases in Liquids:

1- The Nature of the Liquid:

When other conditions are constant, the amount of a given gas that dissolves in a liquid differs according to the type of the latter, for example; the amount of N_2O that dissolves in 1 liter of water (0.39 liter) is different than that dissolves in 1 liter of blood (0.47 liter).

2- The Nature of the Gas:

When other conditions are constant, the amount of the gas that dissolves in a given liquid differs according to the type of the gas, for example, N_2O is 35 times more soluble in blood than nitrogen (N_2).

3- The Pressure of the Gas: (Henry's Law)

When other conditions are constant, the solubility of a given gas in a given liquid is **directly proportional** to the pressure of the gas.

Henry's law states that at a particular temperature the amount of a given gas dissolved in a given liquid is **directly proportional to the partial pressure of the gas in equilibrium with the liquid**.

For example, at a constant temperature, when the atmospheric pressure is doubled, the amount of the gas such as nitrogen is doubled. Therefore, the amount of the gas dissolved in a liquid is also doubled (figure 5-16).

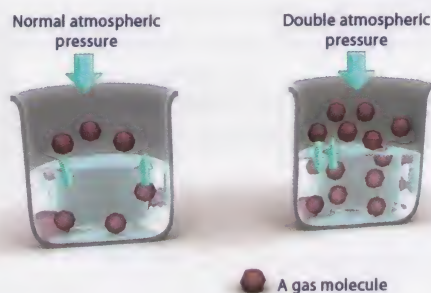


Figure 5-16: Normal atmospheric pressure (left) and double atmospheric pressure (right)

A Clinical application: decompression sickness (the bends) occurs when the sea-divers who are breathing under pressure of the water, return up to the atmospheric pressure too rapidly. The nitrogen comes out of the blood as small bubbles producing gas embolism.

4- The Temperature of the Liquid:

When other conditions are constant, the solubility of a given gas in a given liquid is **inversely** proportional to the temperature of the liquid.

For example: • in a **kettle** about to boil, the simmering which occurs is due to the release of bubbles of air which come out of solution as the water is heated.

• in the operating theater, **bubbles** of air may form in saline in an **infusion line** which has passed through a **blood-warming coil**.

Solubility Coefficients

There are two types of solubility coefficients:

1- Bunsen Solubility Coefficient:

• It is the **volume of gas**, corrected to **standard temperature and pressure (STP)**, which dissolves in 1 unit volume of the liquid at a given temperature (i.e., the temperature of the experiment) where the partial pressure of the gas above the liquid is 1 standard atmospheric pressure.

N.B.: Standard Temperature and Pressure (STP) is the temperature of 273.15 K (0 °C) and the pressure of 101.325 kPa (1 atmospheric pressure).

• This coefficient is **used only in scientific tables and academic works**.

• **For example**, on measuring the gas at a temperature 25 °C and at atmospheric pressure, the volume of the gas which dissolves in 1 unit volume of the liquid is determined e.g., 0.47 L. This gas volume 0.47 L is corrected by equations as if it is measured at STP i.e., the temperature is 0 °C and the pressure is 1 atmospheric pressure. Therefore, the volume will be changed.

2- Ostwald Solubility Coefficient:

• It is the **volume of gas** which dissolves in 1 unit volume of liquid **at a given temperature, independent on pressure**.

• This coefficient is **used in anesthetic practice**.

• Ostwald solubility coefficient does not depend on the pressure. This is explained by the following example: at 100 kPa (1 bar) pressure of nitrogen above the surface of 1 liter of water, a volume of 0.016 liter of nitrogen dissolves in the water. If the pressure of the nitrogen above the water is doubled to 200 kPa (2 bar), the following events will happen:

- According to Henry's law, the quantity of the dissolving gas is proportional to the pressure, so there is twice as much nitrogen dissolved in the water i.e., 0.032 liter if measured at a pressure of 100 kPa.
- According to Boyle's law, when the volume is measured at the ambient pressure (2 bar), the volume of the gas becomes its half i.e. 0.016.

Therefore, the volume of dissolved nitrogen measured at the ambient pressure remains constant even though the partial pressure of the nitrogen is doubled and the number of nitrogen molecules in solution is also doubled.

From the above, the pressure does not affect the volume of the gas that dissolves; provided that the volume is measured at the ambient pressure.

The Partition Coefficient

The partition coefficient **is defined as** the ratio of the amount of a substance present in one phase compared with another; the two phases being of equal volume and in equilibrium

i.e., it is the ratio of $\frac{\text{concentration (amount) of a gas (e.g., anesthetic gas) in one phase}}{\text{concentration (amount) of a gas (e.g., anesthetic gas) in another phase}}$ at equilibrium.

For example, when 1 liter of N₂O is above 1 liter of blood, the amount of N₂O that dissolves in the blood at equilibrium at 37 °C is 0.47 liter (figure 5-17).

Therefore, the blood/gas partition coefficient for N₂O = $\frac{0.47 \text{ liter of N}_2\text{O in the blood}}{1 \text{ liter of N}_2\text{O}} = 0.47$

Similar Aspects between the Ostwald Coefficient and the Partition Coefficient:

1- Both the partition coefficient and Ostwald coefficient are **numerically equal** i.e., both are 0.47 for N₂O in blood.

2- In both the partition coefficient and Ostwald coefficient, the temperature should be specified, but not the pressure.



Figure 5-17: Blood/ gas partition coefficient (left) and blood/oil partition coefficient (right)

Differences between the Ostwald Coefficient and the Partition Coefficient:

1- In the partition coefficient, the relative order of the phases must be clearly identical e.g., for N_2O and blood:

• blood/gas partition coefficient = $\frac{0.47}{1} = 0.47$

while • gas/blood partition coefficient = $\frac{1}{0.47} = 2.1$.

2- The partition coefficient can be applied between two liquids e.g. blood/oil partition coefficient which, at equilibrium, is the ratio of the amount of N_2O present in unit volume of blood to that in unit volume of oil. For example, 1.4 liters of N_2O dissolve in 1 liter of oil, compared with 0.47 liter in 1 liter of blood.

Thus, the blood/oil partition coefficient for N_2O = $\frac{0.47}{1.4} = 0.33$ at equilibrium between the two phases

i.e., the tension of N_2O must be the same in the two phases.

Clinical Applications:

1- Solubility of Inhalational Anesthetic Agents in the Blood:

• The onset of induction and recovery is inversely proportional to the blood/gas solubility coefficient of the anesthetic agent. It is discussed before in pharmacokinetics of inhalational anesthetics; see before in chapter of "Pharmacology of anesthesia and intensive care".

• The effect on closed gas spaces, the concentration effect, the 2nd gas effect, and the diffusion hypoxia (figure 5-18) are discussed in more details in the chapter of "Pharmacology of anesthesia and intensive care".

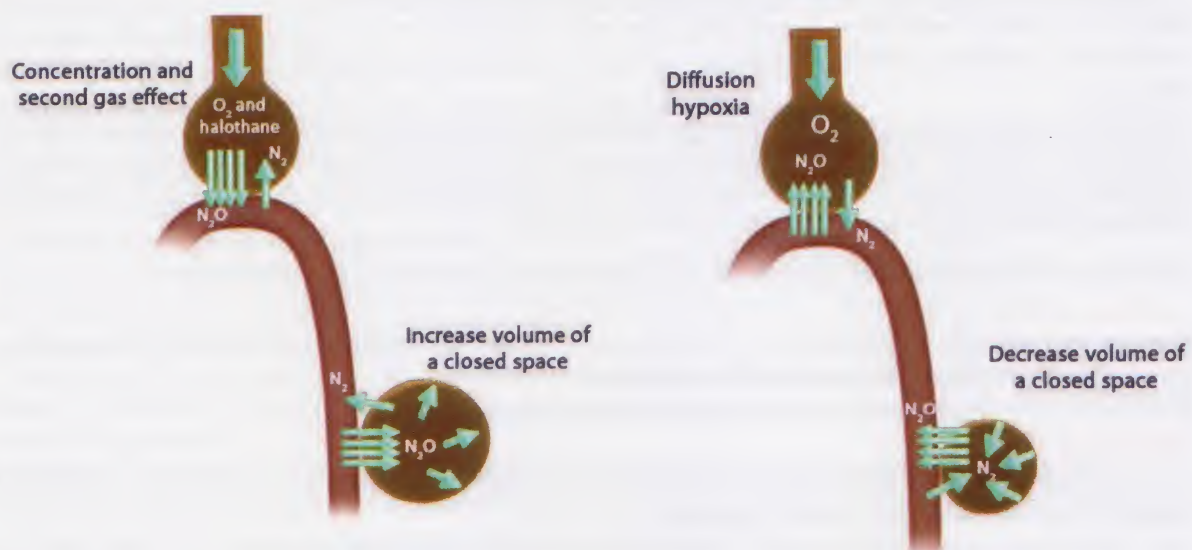


Figure 5-18: The effects on closed spaces, the concentration effect, the second gas effect, and diffusion hypoxia

2- Solubility of Inhalational Anesthetic Agents in Oil:

The **potency** of inhalational anesthetic agents (MAC) is **directly proportional** to the lipid solubility (**oil/gas solubility coefficient**) of the agent. This is called **the unitary hypothesis (Meyer Overton rule)** which has been originally developed in 1901 by HH Meyer & E Overton. It has been suggested that all anesthetics act by this theory (hence, the name unitary).

3- Solubility of Inhalational Anesthetic Agents in Rubber: e.g., breathing circuits.

The **onset of induction and recovery** is **inversely proportional** to the **rubber/gas solubility coefficient** of the anesthetic agent. Increased rubber/gas solubility coefficient of the anesthetic agent slows the onset of induction and recovery. Halothane is 100 times more soluble in rubber than N₂O.

Traces of halothane can be released to another patient on subsequent use of the same anesthetic circuit.

Colligative Properties of a Solution:

These properties of a solution depend on the number of solute particles rather than the type of the particles. An increase in the number of particles (the concentration of the solute) produces:

- Depression of the freezing point.
- Elevation of the boiling point.
- Depression of the vapor pressure.
- Elevation of the osmotic pressure.

On measuring the osmolarity, any of the above properties e.g., depression of the freezing point may be used.

Diffusion

Definition:

Diffusion is the movement of the molecules of a substance **from an area of higher gas pressure to one of a lower pressure** until equilibrium occurs.

This movement can occur through one of the following ways:

- Through a dry porous membrane e.g., an anesthetic agent diffusing across a membrane.
- Through a layer or an area such as the surface of a solution i.e., a gas-liquid barrier e.g., alveolar capillary membrane.
- or • without a membrane or a gas-liquid barrier e.g., if a gas escapes from a broken gas pipe, the gas spreads by diffusion even after the gas tap has been turned off.

N.B.: Bulk Flow:

It is the mass movement of the gas through an orifice or a tube. It cannot occur through fine pores. It does not depend on the molecular weight (as diffusion), but on the density of the gas.

For example:

- In respiration, the movement of the inspired gas from the breathing circuit to the alveolar-capillary membrane during ventilation is bulk flow (its rate = gas flow x gas concentration), but once the gas reaches the alveolar-capillary membrane, diffusion occurs (see below the factors affecting the rate of diffusion).
- In the circulation, the movement of the gas in blood from the alveolar-capillary membrane to the tissues is bulk flow (its rate = blood flow x gas concentration), but from the blood to the interstitial compartment diffusion occurs through the blood vessel walls. Also diffusion occurs from the interstitial compartment to the intracellular compartment through the cell membrane.

Factors Affecting the Rate of Diffusion (Laws of Diffusion)

1- Fick's Law:

It states that the **rate of diffusion** of a substance across unit area (such as a surface or a membrane) is **directly proportional to the concentration gradient**.

This law applies only if the gas is moving in a single homogenous phase.

Modified Fick's Law:

It states that the **rate of diffusion** of a substance across unit area (such as a surface or a membrane) is **directly proportional to the tension gradient**.

This modification applies if the gas is transferring from one phase into another, as in the case of gases passing into solution.

The modified Fick's law is **more relevant in anesthesia** than the original law because it applies universally i.e., through a membrane or between liquids or between a gas and a liquid.

N.B.: The Tension or the Partial Pressure of Gas in a Solution:

At equilibrium, when the partial pressure of N_2O in the gaseous phase above blood is 50 kPa, the tension (the partial pressure) of N_2O in the blood is also 50 kPa i.e., the tension of a gas in a solution is the partial pressure of the gas which would be in equilibrium with it (figure 5-19).

The word tension is often used instead of partial pressure for the gas in the gaseous phase.

The Solubility of the Gas in the Liquid:

When the gas passes into a liquid phase e.g., through the alveolar-capillary membrane, diffusion of the gas depends on the tension or the concentration gradient in the liquid itself. Because solubility has an effect on tension or concentration gradient; therefore, the solubility of the gas in the liquid affects the rate of diffusion. **The greater the solubility of the gas in the liquid, the greater will be the tension or the concentration gradient and so, the rate of diffusion.**

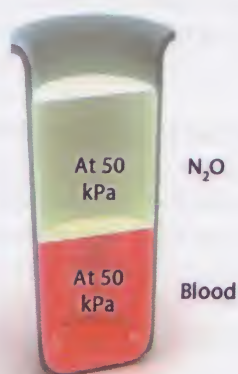


Figure 5-19: Gas tension

- Molecular weight of $O_2 = 32$; therefore, the rate of diffusion $\propto 1/\sqrt{32}$
the rate of diffusion $\propto 1/5.65$
 $1/5.65 = 0.1769$
- Molecular weight of $CO_2 = 44$; therefore, the rate of diffusion $\propto 1/\sqrt{44}$
the rate of diffusion $\propto 1/6.63$
 $1/6.63 = 0.1508$

Therefore, the rate of diffusion of O_2 is greater than that of CO_2 through a dry membrane.

3- The Nature of the Membrane:

Diffusion depends on the nature of the membrane (its area, thickness, and constituents), as membranes vary in their diffusing capacity.

Clinical Aspects of Diffusion**1- Diffusion of O_2 and CO_2 through the alveolar-capillary membrane:**

- The rate of diffusion of O_2 is greater than that of CO_2 through a dry membrane, but the alveolar-capillary membrane is a wet membrane, and the solubility of the gas in water also affects the rate of diffusion. For this reason, CO_2 diffuses faster than O_2 through the alveolar-capillary membrane because CO_2 is 20 times more soluble in water than O_2 .
- The blood normally takes 0.75 second to pass through the alveolar capillary. CO_2 equilibrates in less than 0.1 second while O_2 equilibrates in 0.35 - 0.4 second. The longer time taken by O_2 is due to:
 - slower diffusion compared with CO_2 .

and - removal of O_2 molecules from the plasma as they combine with hemoglobin in the red cells.

Therefore, if diffusing capacity is limited e.g., during pulmonary edema, hypoxia is thus more likely to occur than hypercapnia.

2- Diffusion of anesthetic gases e.g., isoflurane or sevoflurane through corrugated rubber tubes:

Therefore, the rubber tube provides a possible source from which halothane or isoflurane may diffuse into the patient later on inducing malignant hyperthermia although the vaporizer is off.

3- Effect of N_2O on closed gas spaces.**4- Diffusion hypoxia of N_2O .**

Osmosis

Definitions

Osmosis:

It is the net movement of solvent (water) across a semi-permeable membrane due to a difference in non-diffusible solute concentrations between the two sides (figure 5-20).

The semi-permeable membrane separates a solution containing non-diffusible solutes e.g., glucose, which cannot pass through the semi-permeable membrane from a solvent e.g., water which can pass through the membrane.

Osmotic Pressure:

It is the pressure that must be applied to the side with more solute to prevent a net movement of water down the concentration gradient. It is generally **dependent on the number (rather than the type)** of non-diffusible solute particles e.g., ionizing substances exert a greater osmotic pressure than non-ionizing substances as 1 mmol of NaCl exerts an osmotic pressure of 2 mOsmol while protein or glucose exerts less osmotic pressure.

Osmole:

It is the unit which represents **the amount of osmotically active particles present in the solution** e.g.:

a. For non-ionized substances: 180 g glucose or 60 gram urea i.e., molecular weight in gram (one mole) in 1 liter of water represents a solution with a molar concentration of 1 mol/liter and an osmolarity of 1 osmol/liter i.e., **for glucose or urea, one mol/L = one osmol/L.**

Such a molar solution will exert an osmotic pressure of 22.4 atmosphere.

If 1 mole of a gas or a solute is present in a 22.4 liter capacity at a temperature of 0 °C, the osmotic pressure that has built up this compartment is 101.325 kPa or 1 standard atmosphere.

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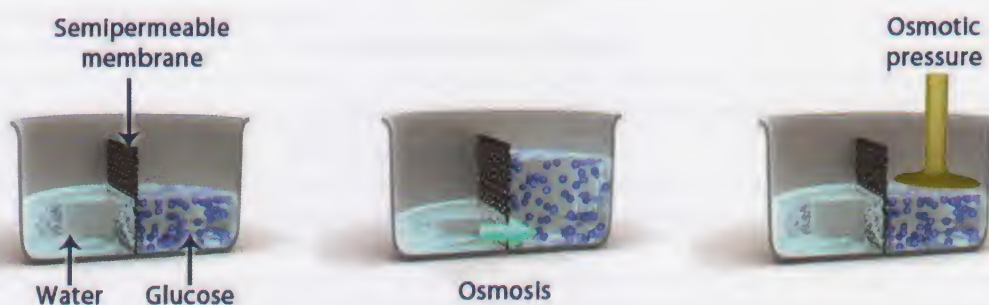


Figure 5-20: Osmosis and osmotic pressure

b. For ionized substances: NaCl ionizes in solution and each ion represents an osmotically active particle i.e., each mole gives n osmoles (where n is the number of ionic type produced)

i.e., MW in grams = one osmole \times number of freely moving particles each molecule liberates in solution.

$$\text{One Osmole} = \frac{\text{Molecular weight in grams}}{\text{Number of freely moving particles each molecule liberates in solution}}$$

Clinical Applications:

Actually, ionic interaction between the cation and anion reduces the effective activity of each, so that NaCl behaves as if it is only 75% ionized.

- Assuming complete dissociation of NaCl into Na^+ and Cl^- , 58.5 gram of NaCl (molecular weight in gram) dissolved in 1 liter of water has a molar concentration of 1 mol/liter and an osmolarity of 2 osmol/liter.

- In body fluids, solute concentrations are much lower (mmol/liter) and their dissociations are incomplete; therefore, a solution of NaCl containing 1 mmol/liter contributes to slightly less than 2 mOsmol/liter

$$\begin{aligned} \text{i.e., for NaCl, one mol/L} &= n \times \text{osmol/L} \\ &= 2 \times \text{osmol/L} = 2 \text{ osmol/L} \\ &= \text{Less than 2 osmol/L in the body fluids.} \end{aligned}$$

Osmolarity: It is the number of osmoles per **liter** of solution (i.e., the volume of solvent) (mass/volume)

i.e., osmol/liter (or osm/L).

Osmolality: It is the number of osmoles per **kilogram** of solution (i.e., the weight of solvent) (mass/mass) i.e., osmol/kg.

N.B.: Osmolarity is affected by the volume of the solute in the solution and by the temperature, while osmolality is not.

Clinical Applications:

• In **body fluids**, both osmolarity and osmolality are nearly **equal**; for example, plasma osmolarity (mOsm/liter) = plasma osmolality (mOsm/kg) = 280-310 because:

- **the solvent** in the body fluid is the **water** which has a density of one i.e., osmol/liter = osmol/kg.

and - **the solutes' volume** contained in biological fluids is **negligible**.

• The **osmolarity of ringer's lactate solution** is the total sum of the following components:

Sodium	131 mmol/liter
Potassium	5 mmol/liter
Calcium	2 mmol/liter
Lactate	29 mmol/liter (assuming that lactate is all in an ionized form)
Chloride	111 mmol/liter

Total osmolarity 278 mOsmol/liter (the sum of the molarities of the solutes)

Plasma Osmolality

It is the number of the osmotically active substances present in 1 kg (or 1 liter in osmolarity) of the plasma.

Measured Plasma Osmolality:

It is the total number of osmotically active substances present in 1 kg of the plasma.

It is measured by an osmometer. Its principle is based on depression of the freezing point. The freezing point of the normal human plasma is -0.54°C , which corresponds to an osmolal concentration of 290 mOsm/L. This is equivalent to an osmotic pressure of 7.3 atmosphere at 37°C .

Calculated Plasma Osmolality:

It is simply calculated as:

$$\begin{aligned}
 &= 2 \times [\text{Na}^+] \text{ mmol/L} + \text{blood glucose mmol/L} + \text{blood urea mmol/L} \\
 &= 2 \times [\text{Na}^+] \text{ mmol/L} + \frac{\text{Blood glucose mg/dL} \times 10}{180} + \frac{\text{Blood urea mg/dL} \times 10}{28} \\
 &= 2 \times [\text{Na}^+] \text{ mmol/L} + \frac{\text{Blood glucose mg/dL}}{18} + \frac{\text{Blood urea mg/dL}}{2.8} \\
 &= 280-290 \text{ mOsmol/L.}
 \end{aligned}$$

The $[\text{Na}^+]$ is multiplied by 2 to include the osmotic contribution of chloride (and Na^+ is the main osmotically active solute present in the plasma "responsible for 50% of plasma osmolality") and its number is nearly equal to the number of the other solutes.

Both glucose and blood urea are chosen to be included in the equation of calculated plasma osmolality because they are important metabolites in both diabetic ketoacidosis and renal failure where calculated plasma osmolality is important.

Plasma Osmolar Gap is the discrepancy (differences) between the measured and calculated osmolarity. Because solutes other than sodium, chloride, glucose, and urea are present in the extracellular fluid, the measured plasma osmolality will be greater than the calculated plasma osmolality. Osmolar gap is normally as much as 10 mOsm/kg H_2O . An increase in Osmolar gap occurs in the following conditions:

- 1- Those receiving large amount of glycine (as during TURP).
- 2- Marked hyperlipidemia or hyperproteinemia
- 3- Chronic renal failure (i.e., retention of small solutes and toxins). In acute renal failure (azotemia), urea is the main accumulated product; therefore normal osmolar gap.
- 4- Ketoacidosis (i.e., high concentration of ketone bodies).
- 5- Other substances and toxins as ethanol, mannitol, methanol, ethylene glycol, or isopropyl alcohol.

Tonicity (Effective Osmolality):

It is the **effect** a solution has on **cell volume**.

It describes the effective osmotic pressure of a solution relative to that of plasma.

- An **isotonic** solution has the same osmolality of plasma and has no effect on cell volume.
- A **hypotonic** solution has less osmolality than plasma and increases cell volume.
- A **hypertonic** solution has more osmolality than plasma and decreases cell volume.

The critical difference between osmolality (a chemical term) and tonicity (a physiological term) is that **all** solutes contribute to osmolality, but only solutes that do not cross the cell membrane contribute to tonicity. Thus **tonicity expresses the osmolar activity of solutes restricted to the extracellular compartment i.e., those which exert an osmotic force affecting the distribution of water between intracellular fluid and extracellular fluid.**

For example:

- **Urea**, ethanol and methanol **diffuse freely** across cell membranes, so they do not contribute to tonicity, but contribute **only to osmolality**.
- Mannitol and sorbitol do **not diffuse** across cell membrane. They are only present in extracellular fluid, therefore, they contribute **to both osmolality and tonicity**.

Plasma osmolality = $2 [\text{Na}^+] \text{ mmol/L} + \text{blood glucose mmol/L} + \text{blood urea mmol/L}$
 = 290 mOsmol/kg.

Plasma tonicity = $2 [\text{Na}^+] \text{ mmol/L} + \text{blood glucose mmol/L}$
 = 285 mOsmol/kg.

Oncotic Pressure

It is the term used to describe the **osmotic pressure exerted by the plasma proteins** (which are restricted to the intravascular compartment) especially albumin because of its higher molar concentration.

The osmolality of the albumin is relatively very small (approximately 1 mOsmol/L) in relation to total plasma osmolality and total osmotic pressure exerted by the plasma (300 mOsmol/L).

The oncotic pressure in the capillary (mainly due to albumin) is about 26 mmHg (3.5 kPa) in the upright position and 20 mmHg in the supine position. The positional change in oncotic pressure is explained by changes in plasma volume as plasma volume decreases 5-25% when changing from supine to standing position where fluid gets out from capillary blood in the lower extremities in response to gravitational increases in capillary hydrostatic pressure. This produces a hemoconcentration effect and increase the concentration of plasma proteins during standing.

Clinical Applications:

Exchange between fluid compartments and capillary fluid exchange (**Starling's forces**) was 1st described in 1896 (figure 5-21).

Starling's forces are described in the following equation: $Q_v = K [(P_c - P_t) - \sigma_c (\pi_{tc} - \pi_{it})]$

Where:

Q_v = total flow of fluid across the capillary membrane.

K = fluid filtration coefficient which reflects the permeability and the surface area of the capillary bed.

P_c = capillary hydrostatic pressure.

P_t = interstitial hydrostatic pressure.

σ_c = reflection coefficient. It is a mathematical expression (from 0 to 1) of the capillary membrane permeability to a particular substance, so it varies with the tissue and the substance filtered. If the capillary membrane is completely permeable to a substance, the reflection coefficient will be 0. If it is totally impermeable to a substance, the coefficient will be 1 e.g., for protein, reflection coefficient in the liver is 0.1, in the lungs it is 0.7 which decreases to 0.4 in case of pulmonary insult i.e., leaky capillary state, and in the brain it is 0.99.

π_{tc} = capillary (plasma) oncotic pressure.

π_{it} = interstitial oncotic pressure.

Normally, all of the fluid filtered is reabsorbed back into the capillaries except 10% of this fluid (about 2 mL/min) which enters the interstitial fluid (and is not reabsorbed), but is then returned by lymphatic flow to the intravascular compartment. Arterial capillary pressure is determined by the precapillary sphincter tone. So, capillaries that require a high pressure such as those in glomeruli have low precapillary sphincter tone while capillaries that require a low pressure such as in muscles have high precapillary sphincter tone.

During resuscitation, if the patient receives large amounts of crystalloids, there will be dilution and hence a decrease of intravascular naturally occurring colloids as albumin and fibrinogen. This decreases the osmotic pressure allowing passage of water from the intravascular to the interstitial space in peripheral tissues, which produces pitting edema.

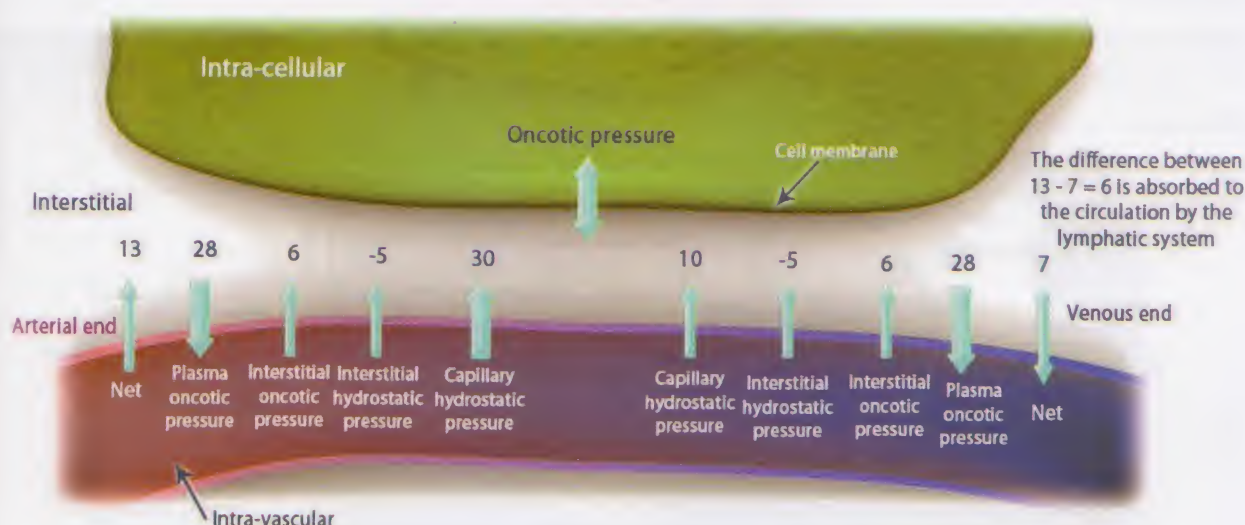


Figure 5-21: Starling's forces

Measurement of Osmolality (by an Osmometer)

Types of the Osmometers:

a- Direct Osmometers:

The sample is put in a thin long tube whose end is covered by a semi-permeable membrane. The tube is immersed in pure distilled water. Water rises in the tube by osmosis until equilibrium occurs (figure 5-22). The hydrostatic pressure of the column of solution in the tube is a measure of the osmotic pressure.

b- Indirect Osmometers: There are two types:

1- Indirect by depression of the freezing point:

Idea: depression of the freezing point of a solution e.g., plasma or urine is directly proportional to its osmolality.

The device:

- The urine or plasma sample is put in the sample tube which is present in the refrigerator bath. There are also a temperature measuring probe and a vibrating stirrer in the sample tube.
- The temperature of the sample falls below the freezing point (i.e., supercooling) due to the refrigerator effect. The vibrating stirrer is used to initiate freezing after supercooling has occurred.

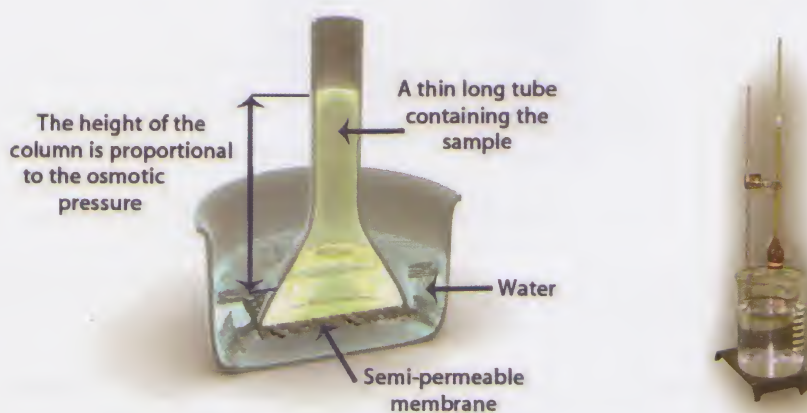


Figure 5-22: A direct osmometer

- The sample gets warmer gradually until a steady freezing point temperature is reached where the solution changes become steady (figure 5-23).

Addition of 1 mole (1000 mmole) of a substance to 1 liter of water depresses the freezing point by 1.86 °C i.e., 1000 mOsmol/L depresses the freezing point by 1.86 °C.

As plasma depresses the freezing point by 0.54°C ; therefore, plasma osmolarity can be calculated.

1000 mOsmol/L depresses the freezing point 1.86°C

X mOsmol/L depresses the freezing point by 0.54°C

Therefore,
$$X = \frac{1000 \times 0.54}{1.86} = 290 \text{ mOsmol/L}$$

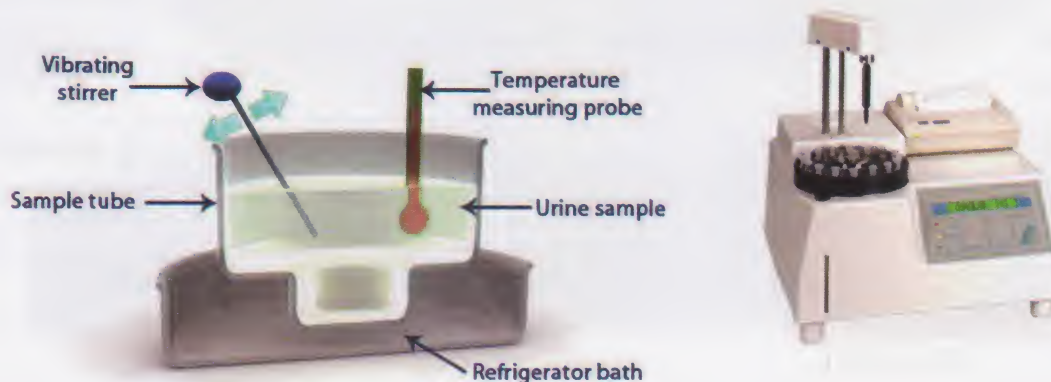


Figure 5-23: An indirect osmometer

2- Indirect by depression of the vapor pressure:

Idea: **Raoult's law** states that the depression or reduction of vapor pressure of a solvent is inversely proportional to its osmolarity.

Presence of large solute molecules reduces the surface area available for the escape of the smaller solvent molecules. Therefore, the vapor pressure of the solvent decreases (figure 5-24).

The indirect methods depend on **the colligative properties of a solution**.....see above.

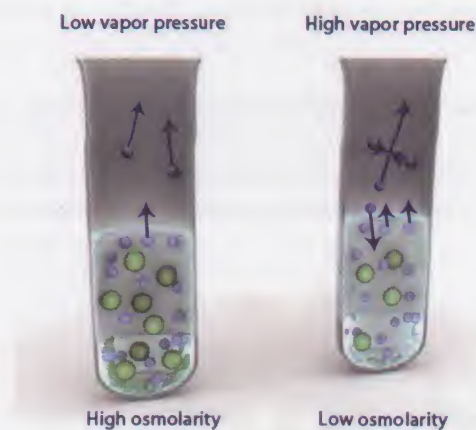


Figure 5-24: Raoult's law

Azeotropes

It is an application to **Raoult's law**. An azeotrope is a mixture of two liquids which vaporizes in the same proportion as the volume concentrations of the components of the liquids.

For example,

- A mixture of ether and halothane is an azeotrope. If there is 1 volume of ether and 2 volumes of halothane in the azeotrope, the ratio of their molar concentrations will be 1 to 2 and so, by Raoult's law, the vapor pressure will also be in the same proportion.

- A mixture of 96% alcohol and 4% water form an azeotrope which evaporates in the ratio of 96 parts of alcohol to 4 parts of water.

Part 4: GAS LAWS

Molecular Theory

A substance may be present in one of three forms (figure 5-25):

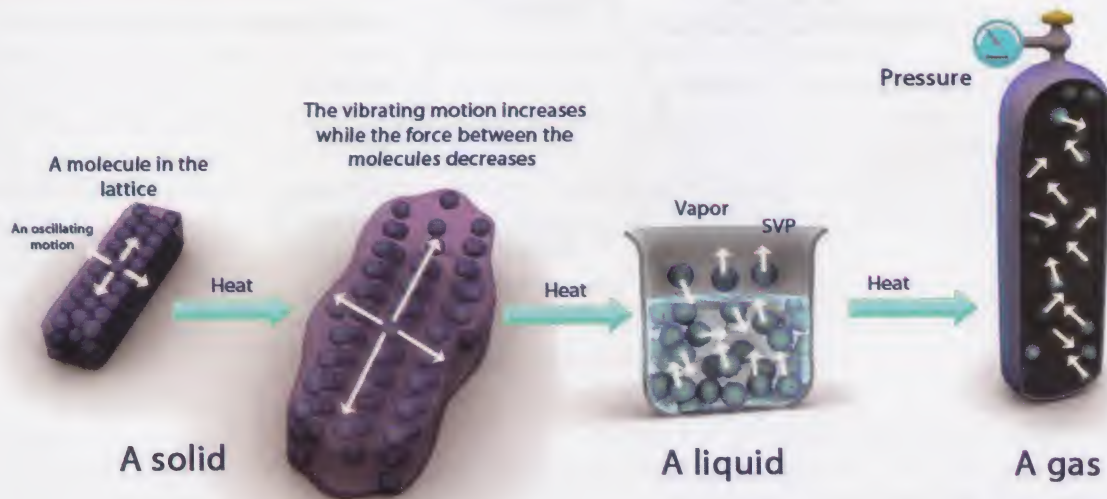


Figure 5-25: The molecular theory

	Solids	Liquids	Gases
The shape and volume	They have a fixed volume and shape . The atoms or molecules of the solid are usually arranged in a regular formation called a lattice .	They have a fixed volume , but no shape as they take the shape of the container.	They have neither shape nor volume.
The forces between the molecules	Each molecule in the lattice exerts forces on its neighbors.	The molecules still exert some forces of attraction on each other. This force is called van der Waals forces .	The force between the molecules is very minimal or absent, but the molecules collide with each other and with the walls of the container. These collisions exert a force on a certain area of the walls. This force is called the pressure .
The motion of the molecules	Each molecule continuously oscillates or vibrates around a fixed point .	The molecules in a liquid have more vibrational motion than in solids and each molecule can move about through the liquid .	Each molecule moves completely independent from its neighbors.
If heat is added,	Molecules move further apart and the forces exerted on their neighbors decrease. Eventually, the forces are not sufficient to hold the molecules together in a lattice. Therefore, the lattice breaks into smaller groups. With further increasing of heat, lattice completely breaks and the solid substance melts to a liquid i.e., melting process occurs.	Each molecule gains more kinetic energy and eventually some molecules are able to overcome the van der Waals forces and are able to move in the space as a vapor or a gas i.e., evaporation occurs. In the same time, other molecules may enter again in the liquid. At any temperature, equilibrium occurs between those molecules that escape from the liquid to the vapor and those that enter into the liquid from the vapor. The vapor above the liquid is at its saturated vapor pressure (SVP) .	<ul style="list-style-type: none"> If further heat is added boiling point is reached and molecules gain a great energy where the liquid is changed to a gaseous form i.e., boiling process. N.B.: Both liquids and gases are called fluids because their molecules can flow freely.

There are 3 gas laws (figure 5-26):

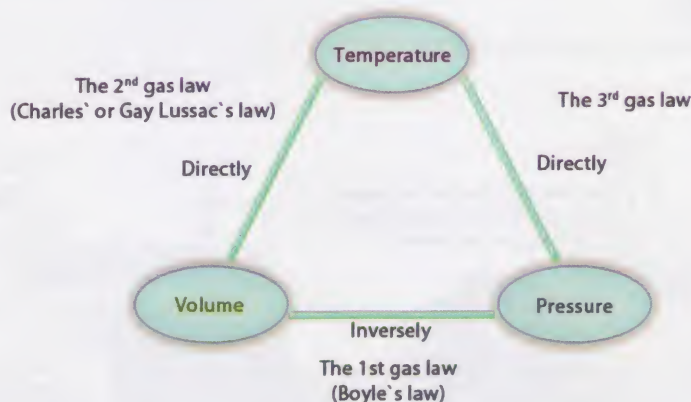


Figure 5-26: Gas laws

I) The First Gas Law (Boyle's Law):

Boyle's law states that at a constant temperature, the **volume** (V) of a given mass of a gas varies **inversely** with the absolute **pressure** (P).

i.e., $V \propto 1/P$

$$VP = \text{constant } (k_1) \quad \text{or} \quad V_1 P_1 = V_2 P_2$$

Clinical Application:

- Calculation of the amount of O₂ that will be available at atmospheric pressure from an O₂ cylinder:

When the 10 liter O₂ cylinder is full, its gauge pressure will be about 137 bar or 13 700 kPa. If the atmospheric pressure is 100 kPa, the total or absolute pressure of the O₂ will be 13 800 kPa.

N.B.: Total or absolute pressure = gauge pressure + atmospheric pressure.

$$\text{As } V_1 \times P_1 = V_2 \times P_2$$

$$\text{Therefore, } 10 \times 13\,800 = V_2 \times 100$$

$$\text{So, } V_2 = \frac{10 \times 13\,800}{100} = 1380 \text{ liters.}$$

As the volume of the empty cylinder is 10 liters, so the amount of O₂ available at the atmospheric pressure is 1380 - 10 = 1370 liters.

II) The Second Gas Law (Charles' Law or Gay Lussac's Law):

This law was discovered by Jacques Charles in 1787 (who did not publish it), but it was published by Joseph Gay Lussac in 1808.

Charles' law states that at a constant pressure, the **volume** (V) of a given mass of a gas varies **directly** with the absolute **temperature** (T).

i.e., $V \propto T$

$$V = \text{constant } (k_2) \times T$$

N.B.: Absolute temperature (K) = temperature (°C) + 273

N.B.: When a given mass of a gas is heated or cooled at a constant pressure, its **volume increases or decreases by 1/273 of its original volume at 0 °C for each degree** rise or fall in temperature respectively.

Therefore, according to Charles' law, at temperature of - 273 °C (or 0 Kelvin), the volume of the gas should fall to zero. This does not occur because the gas liquefies before reaching that temperature. Therefore, Charles' law fails.

Charles' law can be stated as follows; at a constant pressure, the volume of a given mass of a gas expands by 1/273 of its original volume for every 1 °C rise of temperature and vice versa.

Clinical Application:

- According to this law, gases expand when they are heated and, so become **less dense**. Therefore, **warm air tends to rise** and this causes **convection currents**.

III) The Third Gas Law:

The third gas law states that at a constant volume, the absolute **pressure** (P) of a given mass of a gas varies **directly** with the absolute **temperature** (T).

i.e., $P \propto T$

$$P = \text{constant } (k_3) \times T$$

N.B.: When a given mass of a gas is heated or cooled at a constant volume, its pressure increases or decreases by $1/273$ of its original pressure at 0°C for each degree rise or fall in temperature respectively.

Clinical Applications:

- In the **hydrogen thermometer**, when a constant volume of hydrogen is heated, the pressure rises which can be accurately recorded and gives an indication of the absolute temperature.
- A full O_2 cylinder is filled at 137 bar (absolute pressure) at ambient temperature of 17°C (i.e., $17 + 273 = 290$ Kelvin). This cylinder is tested in the factory to withstand pressure up to 210 bar. When the temperature of the cylinder is doubled (i.e., $290 \times 2 = 580$ Kelvin) e.g., **when the cylinder is accidentally dropped on a fire of an incinerator**, the pressure inside the cylinder will be doubled (i.e., $137 \times 2 = 274$ bar) which exceeds the upper limit of the cylinder; therefore, there will be a danger of explosion.

Universal Gas Constant:

By combining the 3 gas laws together:

$$\text{As } VP = \text{constant } (k_1)$$

$$V = \text{constant } (k_2) \times T \text{ i.e., } V/T = \text{constant } (k_2)$$

$$P = \text{constant } (k_3) \times T \text{ i.e., } P/T = \text{constant } (k_3)$$

$$\text{Therefore, } \frac{PV}{T} = \text{constant}$$

For 1 mole of any gas, $\frac{PV}{T}$ = a unique constant known as the **universal gas constant (R)** ($R = 0.082$)

i.e., for 1 mole of any gas, $PV = RT$

i.e., for any amount of the gas, $PV = nRT$

where n is the number of moles of the gas.

This equation is called the **ideal gas law**.

An ideal gas or perfect gas is that which obeys the 3 gas laws. No gas is ideal because under certain conditions a gas may not obey the gas laws.

Clinical Application:

- **The content gauge of a gas cylinder:**

In any cylinder containing a gas, the previous equation can be applied as follows:

As the volume of the cylinder is constant, V in the equation is **constant**.

As the cylinder is in a constant temperature, T in the equation is **constant**.

As R is the universal gas **constant**.

Therefore, the pressure (P) recorded from the gauge pressure of the cylinder is **directly proportional** to the number of moles (n) and thus to the amount of the gas in the cylinder. Therefore, the pressure gauge acts as a content gauge provided that the cylinder contains a gas.

Conditions of Measuring the Volume of Gases

Because the volumes of gases are greatly affected by changes of temperature and pressure, it is important to specify the temperature and pressure at which any measurement of volume is made.

There are 3 common conditions in which the gases are measured.

- **Standard Temperature and Pressure (STP):**

The gas is measured at:

- Temperature = 0°C (273.15 K)
- Pressure = 760 mmHg (1 atmospheric pressure or 101.325 kPa)
- Water vapor pressure = zero

STP is used for measuring O_2 consumption and CO_2 production.

- **Body Temperature and Pressure Saturated (BTPS):**

The gas is measured at:

- Temperature = 37°C
- Pressure = 760 mmHg (1 atmospheric pressure or 101.325 kPa)
- Water vapor pressure = 47 mmHg

BTPS is used for measuring lung volumes and ventilation.

- **Ambient Temperature and Pressure Saturated (ATPS):**

The gas is measured at:

- Temperature = 20°C
- Pressure = 760 mmHg (1 atmospheric pressure or 101.325 kPa)
- Water vapor pressure = 47 mmHg

ATPS is used for measuring inspiratory and expiratory flow rates.

Avogadro's Hypothesis

Avogadro's hypothesis states that **equal volumes** of gases at the same temperature and pressure contain **equal numbers of molecules** (figure 5-27).

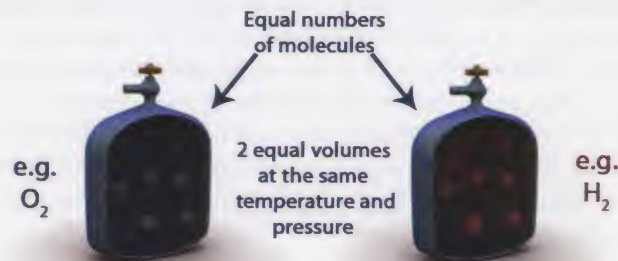


Figure 5-27: Avogadro's hypothesis

A **mole** is the quantity of a substance that contains the same number of particles as the number of atoms in 0.012 kg of carbon 12 i.e., a mole contains 6.022×10^{23} particles. This number is known as **Avogadro's number**.

Mole = molecular weight in grams = 6.022×10^{23} particles.

1 mole of any gas at STP occupies 22.4 liters, for example,

MW of hydrogen (H_2) is (1×2) i.e., 2, so its mole equals 2 grams which occupy 22.4 liters at STP.

MW of oxygen (O_2) is (16×2) i.e., 32, so its mole equals 32 grams which occupy 22.4 liters at STP.

1 mole of any gas at room temperature (20 °C) occupies 24 L.

N.B.: **Led Schumit's number:**

1 cm³ of ideal gas contains 2.7×10^9 molecules.

Clinical Applications:

1- For calibration of a vaporizer (calculation of the concentration of the anesthetic gas):

For example, if a steady stream of O_2 flows into a vaporizer containing 18.45 grams of isoflurane and this amount is completely vaporized into 224 liters, what will the concentration of the isoflurane be?

The molecular weight of isoflurane is 184.5,

so 1 mole (184.5 grams) of isoflurane will occupy 22.4 liters at STP.

Therefore, 18.45 grams in the vaporizer are equal to 0.1 mole and would occupy 0.1×22.4 liters i.e., 2.24 liters.

As the isoflurane has been vaporized into a volume of 224 liters, the concentration of the isoflurane will be $2.24/224$ i.e., 1%

If measurement of isoflurane is done at temperature and pressure other than STP, suitable corrections should be made.

2- For estimation of the consumption of an anesthetic liquid in an anesthetic vaporizer:

For example, if 1% isoflurane is used for 1 hour with a total flow of 8 liters/minute, how many milliliters of liquid isoflurane are used at room temperature in the hour?

• At first, calculate the volume produced by 1 ml isoflurane.

As The density of isoflurane is 1.5 g/mL

Molecular weight of isoflurane is 184.5

1 mole (184.5 grams) of isoflurane occupies 24 liters of vapor at room temperature i.e., 20 °C

1.5 grams (1 mL) of liquid isoflurane occupy X

$$\text{So, } X = \frac{24 \times 1.5}{184.5} = 0.195 \text{ L} = 195 \text{ mL.}$$

i.e., 1 mL of liquid isoflurane gives 195 mL of isoflurane vapor.

$$\text{i.e., } X = \frac{24 \times 1000 \times \text{density}}{\text{grammolecular weight}}$$

Where "1000" is to change from liter to milliliter.

- Secondly, calculate the total volume of isoflurane produced/min.

As 1 % isoflurane is used, this 1 % represents $= \frac{8 \times 1}{100} = 0.08$ L of isoflurane vapor/min.

$$\text{i.e., the total volume of isoflurane/min} = \frac{\text{Flow L/min} \times \text{concentration} \times 1000}{100}$$

Where "1000" is to change from liter to milliliter.

Therefore, the amount of isoflurane used in mL/min

$$= \frac{\text{the total volume of isoflurane/min}}{\text{the volume produced by 1 mL isoflurane}}$$

$$= \frac{\text{Flow L/min} \times \text{concentration} \times 1000 \times \text{grammolecular weight}}{100 \times 24 \times 1000 \times \text{density}}$$

$$= \frac{\text{Flow L/min} \times \text{concentration} \times \text{grammolecular weight}}{100 \times 24 \times \text{density}}$$

$$= \text{Flow (L/min)} \times \text{concentration} \times \frac{\text{grammolecular weight}}{100 \times 24 \times \text{density}}$$

As $\frac{\text{grammolecular weight}}{100 \times 24 \times \text{density}}$ is constant for each inhalational agent.

Therefore, Anesthetic liquid in mL/min = Fresh gas flow (L/min) \times concentration \times constant

The constant of halothane	= 0.054	(The MW of halothane is 197 and the density is 1.5 g/mL)
of isoflurane	= 0.050	(The MW of isoflurane is 184.5 and the density is 1.5 g/mL)
of sevoflurane	= 0.055	(The MW of sevoflurane is 200 and the density is 1.52 g/mL)
of desflurane	= 0.0477	(The MW of desflurane is 168 and the density is 1.465 g/mL)

For example, the amount of isoflurane used/min = $8 \times 1 \times 0.05 = 0.4$ mL/min.

Therefore, the amount of isoflurane used/hour = $0.4 \times 60 = 24$ mL/hour.

3- For calculation of the amount of a gas in a cylinder:

For example, if a typical full N₂O cylinder contains 3.4 kg of N₂O, what is the volume of N₂O obtained from this cylinder?

The molecular weight of N₂O is 44

So, 1 mole (44 grams) of N₂O will occupy 22.4 liters of N₂O vapor at STP.

Therefore, 3400 grams of N₂O will occupy X liters of N₂O vapor at STP.

$$X = \frac{22.4 \times 3400}{44} = 1730 \text{ liters of N}_2\text{O vapor at STP}$$

or 1 mole (44 grams) of N₂O will occupy 24 liters of N₂O vapor at room temperature i.e., 20 °C.

Therefore, 3400 grams of N₂O will occupy X liters of N₂O vapor at room temperature.

$$X = \frac{24 \times 3400}{44} = 1854 \text{ liters of N}_2\text{O vapor at room temperature.}$$

N.B.: The weight of N₂O cylinder is used to indicate the fullness of N₂O cylinder. The **weight of an empty nitrous oxide cylinder** is known as the **tare weight** and is stamped on the top of the cylinder. Therefore, by weighing the cylinder the N₂O content can be calculated.

Dalton's Law of Partial Pressure (by John Dalton)

Dalton's law states that; in a mixture of gases the pressure exerted by each gas is the same as that it would exert if it occupied the container.

Or in other words; the total pressure of a mixture of gases is equal to the sum of the partial pressures of the individual component gases.

Explanation: Pressure in the container is related to the frequency of collision of the molecules with the wall of the container. In a mixture, each type of molecules behaves almost independently of its neighbor;

therefore, the pressure caused by any type of molecules is the same whether the other type of molecules is present or not i.e., there is no effect for the other types of molecules on each other.

Therefore, **the total pressure** exerted on the walls of the container is **the sum of the partial pressures** exerted by all types of molecules according to the number of their molecules (i.e., their concentrations) that collide with the walls of the container without affecting each other.

Clinical Applications:

1- Calculation of the partial pressure of a gas in a mixture:

For example;

- An Entonox cylinder consists of 50% N₂O and 50% O₂. If the cylinder is emptied to an ambient pressure of 100 kPa, the pressure inside the emptied cylinder i.e., 100 kPa = 50 kPa exerted by N₂O + 50 kPa exerted by O₂.

The partial pressure of one gas component = total pressure x fractional concentration of each gas

- A compressed air cylinder consists of 79% N₂ and 21% O₂ (with ignoring the presence of other inert gases). If the cylinder is compressed at a pressure of 100 bar, the pressure exerted by N₂ = 100 bar x 79/100 = 79 bar, the pressure exerted by O₂ = 100 bar x 21/100 = 21 bar.

2- Manufacturing a cylinder containing 10% CO₂ in O₂ mixture:

The cylinder is first filled with CO₂ to an absolute pressure of 13.8 bar. At this pressure, CO₂ is still gaseous at room temperature. O₂ is then added to a total absolute pressure of 138 bar. The overall percentage of CO₂ is then 10%; the same as the ratio of the pressure.

3- Determination of the partial pressure of gases (O₂, N₂, and water vapor) in the atmospheric air during breathing:

The partial pressure of gases is directly proportional to their concentrations in the atmospheric air.

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Isothermal and Adiabatic Changes

For applying the three gas laws, heat energy is required to be added to or taken from a gas as the change in the volume or the pressure of the gas occurs.

Isothermal Changes	Adiabatic Changes
<ul style="list-style-type: none"> • During slow compression or expansion (change of volume) of a gas, heat leaves or enters the surrounding medium; therefore, the temperature of the gas remains constant i.e., an isothermal condition. <p>This condition obeys Boyle's law i.e., when the temperature is constant, there is inverse relationship between the volume and the pressure (VP= constant).</p> <p>In other words,</p> <ul style="list-style-type: none"> • When a gas is slowly compressed, it releases heat which goes off into the surrounding medium; therefore, the temperature of the gas remains constant. • When a gas expands slowly, it absorbs heat from the surrounding medium; therefore, the temperature of the gas remains constant. 	<ul style="list-style-type: none"> • During sudden compression or expansion (change of volume) of a gas, there will be no time for heat to leave or enter the surrounding medium; therefore, the temperature of the gas changes i.e., an adiabatic condition. <p>This condition does not obey Boyle's law.</p> <p>In other words,</p> <ul style="list-style-type: none"> • When a gas is suddenly compressed, there will be no enough time for the gas to release heat into the surrounding medium; therefore, the temperature of the gas will increase. • When a gas expands suddenly, there will be no enough time for the gas to absorb heat from the surrounding medium; therefore, the temperature of the gas will decrease.

Clinical Applications:

1- If a gas cylinder connected to an anesthetic machine is turned on quickly, the gas is suddenly compressed (the pressure of gas in the connecting pipes and gauges rises rapidly) i.e., the gas is compressed adiabatically; therefore, the temperature increases greatly with an associated risk of fire.

2- The cryoprobe:

It is used for rapid freezing of tissues e.g., in **cryoanalgesia** where local degeneration of nerve bundles occurs to produce long-term (3-6 months) analgesia which is used in treatment of chronic pain. N₂O or CO₂ gas is allowed to expand suddenly out of a capillary tube in the cryoprobe tip i.e., an adiabatic expansion. No enough time is allowed for the gas to absorb heat from the surrounding medium; therefore, the temperature of the gas decreases greatly up to - 70 °C.

Critical Temperature and Pressure

Definitions:

• **Critical temperature** is defined as the temperature, above which a substance cannot be liquefied however much pressure (alone) is applied, or it is the temperature to which a gas must be cooled before it can be liquefied by the pressure alone. Critical temperature is applied to a single gas (not a gas in a mixture).

• **Critical pressure** is defined as the vapor pressure of a substance at its critical temperature.

For example, critical temperature & critical pressure

$\text{N}_2\text{O} = 36.5^\circ\text{C}$ 72.5 bar

$\text{CO}_2 = 31^\circ\text{C}$ 73.8 bar

$\text{O}_2 = -119^\circ\text{C}$

$\text{N}_2 = -147^\circ\text{C}$

Air = -141°C

Isotherms

They are graphs that show the relationship between pressure and volume at a constant temperature. Each graph is drawn at a certain constant temperature.

For example, **isotherms for nitrous oxide** (figure 5-28).

There are 3 isotherms drawn for N_2O :

1- An isotherm at 40°C :

As the volume of the gas is reduced, the pressure increases smoothly producing a rectangular hyperbola (according to Boyle's law) i.e., at this temperature the gas obeys Boyle's law.

Above and below this line, gas is formed.

2- An isotherm at 36.5°C (i.e., at the critical temperature and critical pressure):

At 36.5°C , when the volume of the gas is reduced the pressure increases gradually until it reaches 72.5 bar. At this critical pressure, the N_2O liquefies. Because a liquid is relatively incompressible, a further small decrease in volume is associated with a great increase in pressure and an almost vertical line is drawn (it does not obey Boyle's law).

Above this line, gas is formed, but below this line, vapor is formed at large volumes and liquid is formed at small volumes while vapor and liquid are present at the volumes in between.

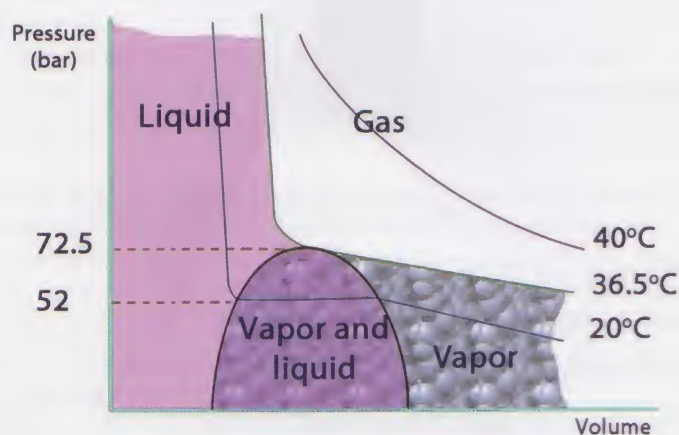


Figure 5-28: Isotherms of N_2O

3- An isotherm at 20°C (i.e., at room temperature):

• As the volume of the gas is reduced, the pressure increases at first gradually until it reaches 52 bar. At 52 bar, some of N_2O liquefies producing both vapor and liquid.

• With a further decrease in the volume, more N_2O vapor is condensed to N_2O liquid; therefore, the pressure remains constant and a horizontal line is drawn (a plateau). This is the pressure of N_2O cylinder at room temperature (being the saturated vapor pressure) where both the vapor and liquid are present in the cylinder and any change from the liquid to the vapor form is not accompanied by a change in the gauge pressure of N_2O cylinder (it does not obey Boyle's law).

• With a further decrease in the volume, more N_2O vapor is condensed to N_2O liquid until all the vapor is changed to a liquid. Any further attempt to reduce the volume is associated with a sharp increase of the pressure and an almost vertical line is drawn (it does not obey Boyle's law). Above and below this line, vapor is formed at large volumes, and a liquid is formed at small volumes while liquid and vapor are both present at the volumes in between.

Therefore, a **gas** form of a substance is present **above its critical temperature**, whereas; a **vapor** form of a substance is present **below its critical temperature**.

At usual room temperature, O_2 (-119°C) and N_2 (-147°C) are gases while N_2O (36.5°C), CO_2 (31°C), halothane and isoflurane are vapors.

N.B.: All gases obey the gas laws perfectly, but when the temperature of the gas approaches its boiling point, the gas does not obey the gas laws.

Clinical Applications:

On filling the gas cylinders in the factory: e.g., N_2O cylinders:

The manufacturers always partially fill the N_2O cylinder with N_2O to leave a volume of N_2O vapor above the liquid (figure 5-29) because if the temperature of the cylinder is increased e.g., in hot weather, the volume of the liquid will expand and compress the vapor above. At the same time, some of the vapor condenses keeping the pressure inside the cylinder constant.

If the N_2O cylinder is filled completely with the liquid, any increase in the temperature will be accompanied with expansion of the liquid, which is incompressible, so the pressure of the cylinder will greatly increase with a great risk of explosion.

The manufacturers use the filling ratio to fill the gas cylinders.

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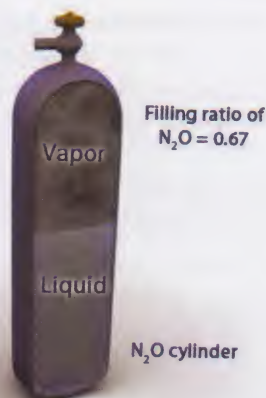


Figure 5-29: N_2O Cylinder

$$\text{Filling ratio} = \frac{\text{The mass of gas in a cylinder}}{\text{The mass of water which will fill the cylinder}}$$

As 1 liter of water weighs 1 kilogram; therefore,

$$\text{Filling ratio} = \frac{\text{The mass of gas in kilograms}}{\text{The internal volume of the cylinder in liters}}$$

For example, the filling ratio of N_2O is 0.67

N.B.: There is a difference between the filling ratio and the volume of liquid N_2O in a cylinder.

A full cylinder of N_2O at room temperature is filled with a liquid to about 90% of the interior of the cylinder while the remaining 10% are occupied by the N_2O vapor.

For example, if the cylinder can hold 100 liters of water,

$$\text{the filling ratio} = \frac{67 \text{ kilograms } \text{N}_2\text{O liquid}}{100 \text{ liters } \text{H}_2\text{O}} = 0.67$$

but the volume of 67 kilogram N_2O liquid is about 90 liters.

Pseudo-Critical Temperature

Definition:

Pseudocritical temperature is the temperature at which the gas mixture may separate out into its constituents.

Pseudocritical temperature changes according to the pressure of the mixture.

Clinical Applications:

Entonox is a mixture of 50% N₂O and 50% O₂.

N₂O does not liquefy at its critical temperature (36.5 °C) because N₂O dissolves in O₂ (also O₂ dissolves in N₂O) at high pressure. In other words, O₂ reduces the critical temperature of N₂O.

Entonox is supplied in either:

a- Entonox cylinders:

The mixture of 50% N₂O and 50% O₂ is compressed inside the cylinder at a pressure of **137 bars**.

The pseudocritical temperature of Entonox in the cylinder is **- 7 °C at 137 bar**
and **- 5.5 °C at 117 bar**

i.e., below these temperatures, N₂O liquid separates from O₂. Therefore, if the Entonox cylinder is used at these low temperatures e.g., during mountain rescue operations, O₂- rich gas is initially emitted followed by a hypoxic N₂O-rich gas causing hypoxia to the patients.

Therefore, on using Entonox cylinders, they should be used horizontally and kept at a temperature above 5 °C for more than 24 hours.

b- Entonox pipelines:

The mixture of 50% N₂O and 50% O₂ is present inside the pipelines at a pressure of **4.1 bars**. The pseudocritical temperature of Entonox in the pipelines is **< - 30 °C at 4.1 bar** which is a very low temperature. Therefore, there is no risk of separation of the Entonox and so, there is no risk of production of a hypoxic N₂O-rich gas. Supplying Entonox through pipelines is safer.

PART 5: TEMPERATURE

Definitions (Differences between heat and temperature)

Temperature: is the thermal state of a substance which determines whether it will give heat to another substance or receive heat from it.

In other words, it is a measure of the tendency of an object to gain or lose heat.

Heat: is a form of energy that can be transferred from a hotter substance to a colder substance.

This heat energy will be in the form of the kinetic energy of the molecules of the substance.

An explanation:

The difference between heat and temperature is the same as the difference between a solute and its concentration where **heat is the solute and the temperature is the concentration**.

- As the concentration of a solution increases when the solute is added to the solution, the temperature of a substance increases when the heat is added to that substance.
- Also, if the solution with a known concentration (or the substance with a known temperature) is divided into 2 equal parts, each part will have the same concentration (the same temperature) although the quantity of the solute (quantity of the heat) in each part is halved.

Temperature Scales

There are three temperature scales (figure 5-30):

Scale	Symbol	Uses	Remarks
1. Kelvin Scale (absolute)	K Notice that the degree symbol (°) is not used.	<ul style="list-style-type: none"> • It is the SI unit of thermodynamic temperature. • It is used mainly in research works, but is not clinically used. 	<ul style="list-style-type: none"> • Kelvin is 1/273.16 of the thermodynamic temperature of the triple point of water. • It has no minus sign because it has a true zero (unlike °C and °F which have minus signs such as -50 °C or -30 °F). • It is derived from Charles' law: When a given mass of a gas is heated at a constant pressure, its volume increases by 1/273.16 of its original volume for each degree rise in temperature.

			Also, when it is cooled its volume decreases by $1/273.16$ of its original volume for each degree fall in temperature. Progressive cooling of a gas will produce a progressive decrease in the volume of the gas until at -273°C the volume of the gas falls to zero, but actually this does not occur because the gas liquefies before it reaches -273°C . This is called the absolute zero and from this, the Kelvin scale is established. The absolute zero is the lowest temperature it is theoretically possible to attain.
2. Celsius Scale (Centigrade) developed by the Swedish astronomer Andes Celsius in 1742	$^{\circ}\text{C}$	It is the most commonly used unit clinically.	Both Kelvin and Celsius scale have degrees of the same size; therefore, conversion from $^{\circ}\text{C}$ to K is simply by adding 273. Temperature K = temperature ($^{\circ}\text{C}$) + 273 N.B.: This scale was divided into 100 steps and so became known by the Latin equivalent centigrade.
3- Fahrenheit Scale developed by the German physicist Fahrenheit in 1714	$^{\circ}\text{F}$	It is used in some countries as USA. Zero $^{\circ}\text{F}$ = freezing point of ammonium chloride = -17°C	The degree of Celsius scale is different than the Fahrenheit; therefore, for conversion , special equations are needed. Celsius scale $^{\circ}\text{C}$ = $(^{\circ}\text{F} - 32) \times 5/9$ = $^{\circ}\text{F} - 32 \div 1.8$ Fahrenheit scale $^{\circ}\text{F}$ = $(^{\circ}\text{C} \times 9/5) + 32$ = $^{\circ}\text{C} + 32 \times 1.8$

Therefore, the absolute zero = zero K = -237°C = -459°F .
 the melting point = 273 K = 0°C = 32°F .
 the boiling water = 373 K = 100°C = 212°F .

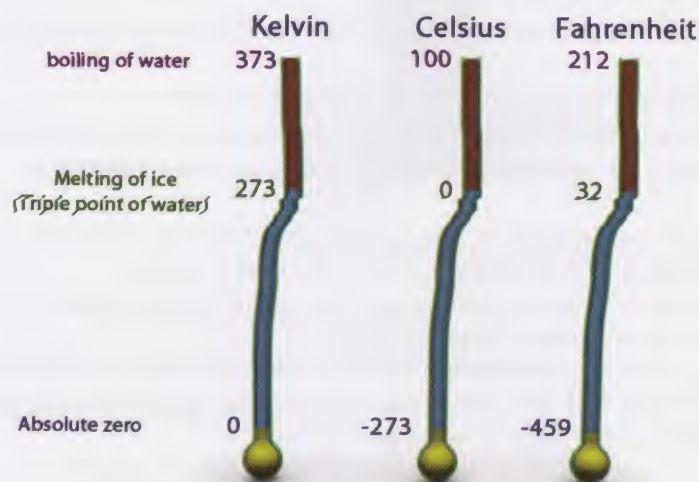


Figure 5-30: Temperature scales

Triple Point of Water:

It is the point (temperature) at which the three phases i.e., solid, liquid, and gaseous phases are in equilibrium.

The triple point of water = 273.16 K = 0.01°C = 32.018°F .

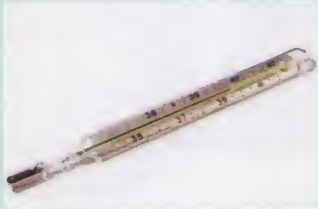
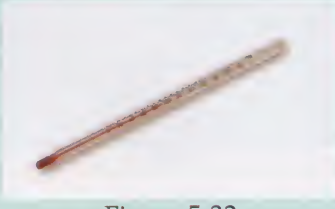
Measurement of Temperature (Thermometry)

All physical properties of the matter are temperature dependent. When heat energy is added to a substance, not only does its temperature rise, but also all its physical properties as viscosity, density,

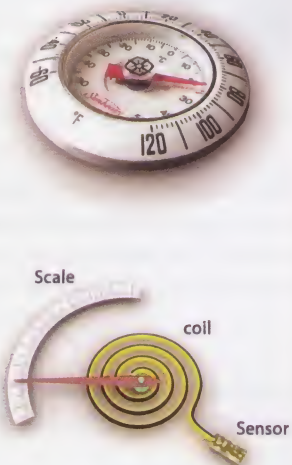
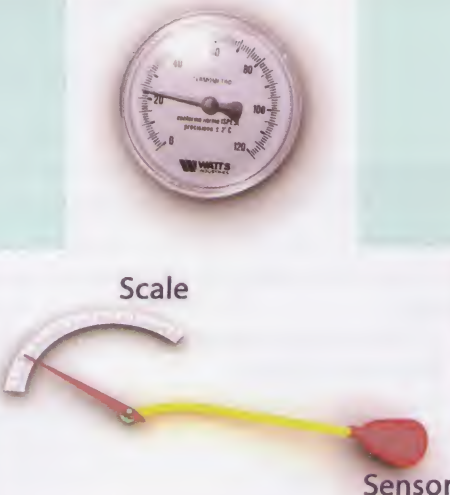
dimensions, electric conductivity, electrical resistance, and elasticity do. Such facts are used in temperature measurement and in the construction of thermometers.

A) Non-Electrical Methods:

1- Liquid Expansion Thermometers:

	Mercury Thermometers	Alcohol Thermometers
Idea	It depends on the phenomenon of change of the volume of mercury with temperature (figure 5-31). 	It depends on the phenomenon of change of the volume of alcohol with temperature (figure 5-32). 
Advantages	<ul style="list-style-type: none"> • It is cheap, so it is the most commonly used in medical practice. • It has a linear scale. • It has a constriction in its capillary tube that permits mercury to expand, but hinders its return to the bulb, so that the reading is preserved until mercury is shaken down. 	<ul style="list-style-type: none"> • It is cheaper than mercury thermometers. • It is more suitable for use at very low temperatures.
Disadvantages	<ul style="list-style-type: none"> • It is unsuitable for remote readings or recording of the results. • It can not be used for very low temperatures because mercury changes to a solid at -39°C. • Its response time is relatively long, about 2-3 minutes, due to high thermal capacity of mercury. • It is difficult to be introduced in some orifices, because of its rigidity, as in nasopharynx. • It is fragile and may break as it is made of glass with risk of injury to the patient. 	<ul style="list-style-type: none"> • It is unsuitable for remote readings or recording of the results. • It is not suitable for high temperatures because the boiling point of the alcohol is 78.5°C. • It has a non-linear scale between the expansion of alcohol and the change of temperature.

2- Dial Expansion Thermometers:

	Bimetallic Strip Thermometers	Bourdon (Pressure) Gauge Thermometers
	 <p>Figure: 5-33</p>	 <p>Figure: 5-34</p>

Idea	Two dissimilar metals, with different coefficients of expansion, are fixed together as a coil. It acts as a sensing element. A rise in the temperature increases the length of the two metals at two different rates which move a pointer on a temperature scale (figure 5-33).	A small bulb containing mercury or a volatile fluid has a small coiled tube which is attached to a pointer. It acts as a sensing element. A rise in the temperature expands the volume and increases the pressure of the mercury or the volatile fluid which in turn moves a pointer on a temperature scale (figure 5-34).
Advantages	• It is cheap.	• It is cheap.
Disadvantages	• It is not accurate. It is used for measuring air temperature.	• It is not accurate. It is used for measuring large temperature changes e.g., in humidifiers, water baths, or autoclaves.

3- Chemical Thermometers:

Idea: A disposable aluminum strip with a transparent cover of multi-cells containing chemical dyes.

A rise of temperature increases the number of cells which release the chemical dyes which in turn appear indicating the temperature.

Nowadays, **reversible chemical thermometers** are available. They contain several cells filled with liquid crystals. At a critical temperature, the optical properties of the crystals change, causing reflection instead of absorption of the incident light.

Advantages:

- It can detect changes of temperature on the skin.

Disadvantages:

- It is disposable, however, this avoids the danger of cross-infection.
- It is not accurate.
- It does not allow remote reading or continuous recording.

B) Electrical Methods:

1- Resistance Thermometer:

Idea: The electrical **resistance** of a metal e.g., a **platinum wire resistor increases with rise of temperature**. Therefore, by measuring the electrical current, temperature can be estimated (figure 5-35).



Figure 5-35: Resistance thermometer

Advantages:

- The calibration of the thermometer is not changed if it is subjected to severe changes of temperature.
- It is very accurate, so it is used for calibration of other thermometers. The increased accuracy is due to the use of an array of temperature sensitive resistors which is incorporated into a **Wheatstone bridge circuit**.
- It allows remote reading and continuous recording.
- The scale is linear.
- The platinum is commonly used because it resists corrosion and equilibrates rapidly with the surrounding temperature.

Disadvantages:

- It has a long response time.
- It is very expensive and fragile.

1- Thermistor:

Idea: The electrical resistance of the thermistor decreases when temperature rises (unlike the thermometer). Some thermistors show an increase in the electrical resistance with a rise in temperature. The thermistor is formed of a small bead of metal oxide e.g., nickel, manganese, cobalt, iron, or zinc oxide (figure 5-36).



Figure 5-36: Thermistor thermometers for esophageal or rectal use (left) and skin use (right)

Advantages:

- The metal oxide bead can be made very small and of different shapes e.g., fixed on a tip of a hypodermic needle.
- It is cheaper than the platinum resistance thermometer.
- The response time is very short, so it can be used for **cardiac output measurement** by thermodynamic technique and to detect changes in temperature between inspired and expired gas.
- It is very accurate. The increased accuracy is due to the use of an array of temperature sensitive resistors which is incorporated into a **Wheatstone bridge circuit**.
- It allows remote reading and continuous recording.

Disadvantages:

- The calibration of the thermistor is changed if it is subjected to severe changes of temperature e.g., during heat sterilization.
- The scale is not linear.
- Thermistors tend to age or show a change in resistance with time.
- Thermistors tend to exhibit hysteresis so that the value of a given temperature recorded during a heating cycle is less than the value recorded at the same temperature during a cooling cycle.

1- Thermocouple:

Idea:

- It is based on the **Seebeck effect**. When two dissimilar metal conductors are joined together to form a circuit, a potential difference (a small voltage) is produced between their two junctions. The potential difference is proportional to the difference in temperatures of the two junctions.
- The two dissimilar metals may be:
 - **Copper and constantan** (constantan is an alloy of 60% copper and 40% nickel).
 - Iron and constantan.
 - Platinum-rhodium.
- One junction (the reference junction) has to be kept at a constant temperature by a thermostatically controlled oven or by insertion in ice water, while the other junction (the measuring junction) acts as a temperature probe (figure 5-37).

Advantages:

- The measuring probe can be made very small; as small as a needle or as a small knob.
- The response time is very short.
- It is accurate.
- It measures a wide range of temperatures.
- It allows remote reading and continuous recording.

Disadvantages:

- The reference junction should be kept at a constant temperature.
- The scale is not linear.

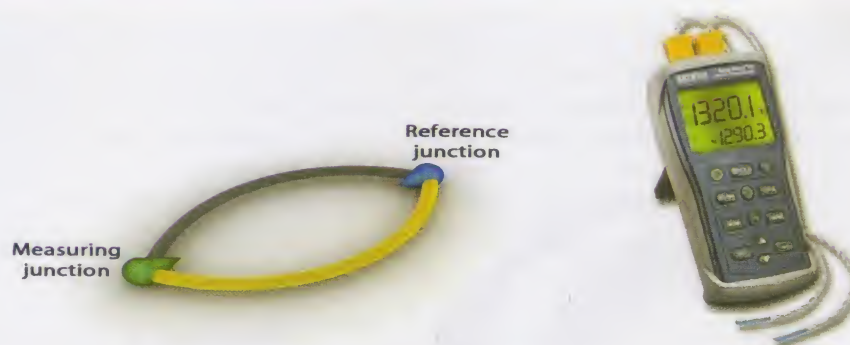


Figure 5-37: A thermocouple

4- Transistor Thermometers:

If a current is passed across transistor junctions, the voltage developed is temperature dependent. It is much more sensitive than thermocouple.

5- Crystal Resonators Thermometers:

The resonance frequency of a quartz crystal is temperature dependent.

6- Optical Thermometers:

Idea:

• Objects emit **electromagnetic radiation**. These radiation waves differ in the wavelength and intensity according to the temperature of the objects. Objects (including the human skin) at body temperature, act as a black-body radiator, so they primarily emit **infrared radiation**. This radiation falls on a sensor (or detector). There are 2 types of sensors:

1- Temperature-sensitive detector: (they are thermistors and thermocouples)

a- **Pyroelectric sensor:** when the radiation falls on the sensor, the temperature of the sensor increases which in turn changes the electric charges of the molecules. This phenomenon is called **polarization**. The change in polarization can be detected as an electrical signal. The electrical signal is proportional to the magnitude of the change of temperature.

b- **Thermopile sensor:** It is formed of many thermocouples or thermistors which are connected in parallel.

2- Photon sensitive detector:

When infrared radiation falls on a photoconductive material such as indium antimonide, a small electrical current is produced. Therefore, the radiant heat from the patient's skin can be imaged by an infrared-sensitive camera to provide a thermograph of the relative warmth of the skin.

Types of Optical Thermometers:

• **Infrared ear thermometer:**

It is a temperature-sensitive thermometer.

It is formed of a tube which is inserted into the ear canal to detect the radiation emitted from the ear canal and the ear drum (figure 5-38).



Figure 5-38: An infrared ear thermometer

• **Tympanic membrane thermometer:**

It is a temperature-sensitive thermometer.

It is formed of a tube which is inserted more deeply into the ear canal to detect the radiation emitted from the ear drum only. Therefore, the temperature is more representative of the core temperature than the ear canal type.

• Thermography:

It is a photon-sensitive thermometer.

Different colors in the thermograph indicate temperature differences and these, in turn, give an indication of the underlying vascularity. Thermographic scanning is used in diagnosing breast tumors, and locating the placenta and vascular occlusion sites.

Advantages:

- They are very sensitive.
- They have a short response time (< 5 seconds).

Disadvantages:

- The pyroelectric sensor can not give continuous reading.

Clinical Applications of Temperature Monitoring

Humans, like all mammals and birds, are **homeothermic** i.e., they control their central body temperature within a narrow range despite a wide range of environmental temperature. In man, this range is normally $37 \pm 0.5^\circ\text{C}$.

Other hibernating animals are **poikilothermic** i.e., their body temperatures are the same as that of the environment.

Body temperature is either (figure 5-39):

- a- **Core temperature:** Temperature of the tissues **deeper than 2.5 cm from the skin**. It includes brain, thoracic and abdominal organs and some deep tissues of the limbs.
- b- **Shell temperature:** Temperature of the tissues within 2.5 cm from the skin. It includes the skin temperature.

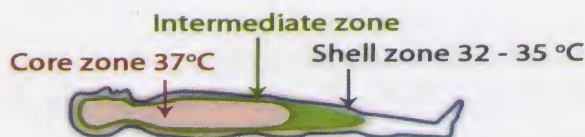


Figure 5-39: Body temperature

Average or mean patient temperature

$$= 0.66 \times \text{core temperature} + 0.34 \times \text{average skin temperature.}$$

Both 0.66 and 0.34 represent the mass of the deep and shell tissues respectively.

Indications of Temperature Monitoring:

Temperature monitoring must be applied for every patient under anesthesia or in intensive care:

- To detect **unintentional** hypothermia e.g., patients who are at risk of hypothermia such as:
 - Surgeries > 15 min.
 - Pediatric patients.
- To detect **peripheral perfusion**; as the **core-peripheral temperature gradient** is the difference between the core and peripheral temperature. Normally, the difference between them $= < 5^\circ\text{C}$. One temperature probe is placed centrally e.g., in the nasopharynx and the other temperature probe is placed peripherally e.g., on the great toe.
- Values - Decreased temperature gradient occurs in peripheral vasodilatation or in high cardiac output.
 - Increased temperature gradient occurs in peripheral vasoconstriction or in low cardiac output.
- To control **elective** hypothermia in cardiac or neurosurgery.
- To detect **hyperthermia** e.g., malignant hyperthermia.

Site of Temperature Measurement (Monitoring):

A) Core Temperature at:

1- The tympanic membrane:

It indicates core temperature (especially **brain** temperature) because the auditory canal's blood supply is the external carotid artery.

It is not routinely used due to risk of **perforation of the drum**.

2- The naso-pharynx:

It indicates core temperature (especially **brain** temperature).

There is a risk of **epistaxis**.

3- The esophagus:

It indicates core temperature (especially **cardiac** temperature).

The thermistor is usually incorporated into the esophageal stethoscope placed in the **lower 1/3 of esophagus** behind the heart because • This avoids measuring the temperature of the tracheal gas.

and • Heart sounds are very prominent at this location (if stethoscope is incorporated).

It is the best, because it is safe and cheap.

4- The rectum:

There is a risk of **rectal perforation** (very rare).

5- **Pulmonary artery** through a pulmonary artery catheter.

6- Urinary bladder.

B) Shell (Peripheral) Temperature:

1- By the **axillary probe**.

2- At the **skin** by liquid crystal adhesive strips (e.g., great toe).

In the neonate, the abdominal skin temperature is very sensitive in detecting a fall of the neonate's temperature.

N.B.: The oral temperature is measured used in awake patients.

Measuring the temperature of the inspired gases is important to avoid thermal burn when an efficient humidifier is used.

PART 6: HEAT**Definition**

When heat is applied to a substance, its temperature rises and when heat is removed from a substance, its temperature falls. See above "Temperature" for the definition and the difference between temperature and heat.

Units of Heat Measurement

The Calorie (cal) is the unit of heat energy. It is the quantity of heat required to raise the temperature of 1 gram of water by 1 °C.

In humans, the calorie is a very minute amount; therefore, **kilocalorie** is used instead.

Kilocalorie is written as follows; kcal, big calorie, or Calorie "with a capital C letter".

Kilocalorie = 1000 calories.

The Joule (J) is the SI unit of heat energy.

1 joule = 0.24 cal

1 cal = 4.2 joule

Kilojoule (kJ) = 1000 joule

Sometimes; **the rate of heat production** is measured by Watt (as 1 Watt = 1 J/s).

Specific Heat Capacity (Specific Heat) and Heat Capacity

Specific heat capacity is often abbreviated to specific heat. It must not be confused with the term **heat capacity**.

Definition:

Specific Heat Capacity: is defined as the amount of heat required to raise the temperature of 1 kilogram of a substance by 1 Kelvin or 1 °C.

SI unit of specific heat capacity: is J/kg/K or J/kg/°C.

Heat Capacity: is defined as the amount of heat required to raise the temperature of a given object by 1 Kelvin or °C.

SI unit of heat capacity: is J/K or J/°C.

Heat capacity = specific heat capacity x the mass of the object.

Quantity of Heat: is defined as the amount of heat required to raise the temperature of a given object by a certain number of Kelvin or Celsius degrees (figure 5-40).

Quantity of heat = specific heat capacity x mass x temperature rise.

N.B.: As both Kelvin and Celsius scales have degrees of the same size; therefore, any one can be used in the definitions above.

N.B.: **Heat Content** = heat capacity \times the mean temperature.

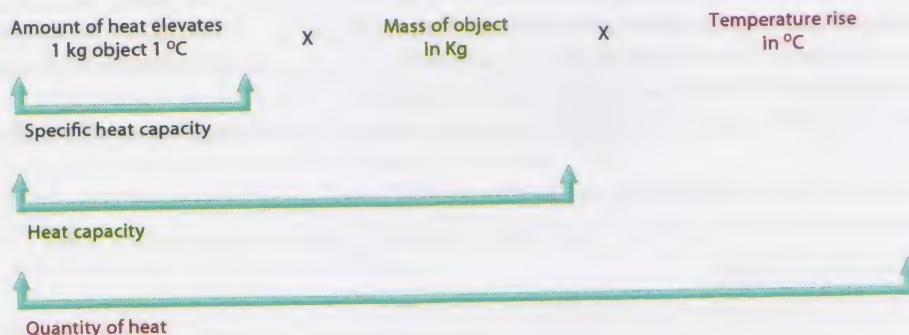


Figure: 5-40: Quantity of heat

Clinical Applications:

1- Specific Heat of Water: $= 4.18 \text{ kJ/kg/}^\circ\text{C} = 1 \text{ kcal/kg/}^\circ\text{C}$

This means that 4.18 kJ or 1 kcal is required to raise the temperature of 1 kg of water by 1°C .

The specific heat of other substances is less than that of water i.e., the specific heat of water is very high; therefore, water can be heated or cooled very slowly. In older anesthetic machines, the water jacket around the Boyle's bottle vaporizer is used as a heat reservoir to prevent rapid fall in the temperature of ether.

2- Specific Heat of Tissues: $\approx 3.5 \text{ kJ/kg/}^\circ\text{C}$

So, the total heat capacity of a 70 kg patient $= 3.5 \text{ kJ/kg/}^\circ\text{C} \times 70 \text{ kg} = 245 \text{ kJ/}^\circ\text{C}$.

3- Specific Heat of Blood: $= 3.6 \text{ kJ/kg/}^\circ\text{C} = 0.87 \text{ kcal/kg/}^\circ\text{C}$

If 2 kg of blood (about 2 liters) are transfused at 5°C to a patient, this cold blood will be warmed up to 35°C in the patient.

Heat required to warm this blood $= 2 \text{ kg} \times 3.6 \text{ kJ/kg/}^\circ\text{C} \times (35-5)^\circ\text{C} = 216 \text{ kJ}$.

As the total heat capacity of a 70 kg patient is $245 \text{ kJ/}^\circ\text{C}$, the patient's mean temperature must fall by up to 1°C when 2 liters of cooled blood are transfused. Therefore, blood warmers are mandatory.

4- Specific Heat of Gases:

The specific heat of a gas is very small compared to that of a liquid or solid i.e., gases can be heated or cooled very quickly. Gases quickly attain the ambient temperature after passing through a short tube.

The quantity of a gas is usually measured in units of volume; therefore, the specific heat of a gas can be expressed as $\text{kJ/L/}^\circ\text{C}$ instead of $\text{kJ/kg/}^\circ\text{C}$.

As the density of gases is very low, the specific heat of gases; when expressed in units of volume, will be very low so:

Specific heat of air $= 1.01 \text{ kJ/kg/}^\circ\text{C}$ at a constant pressure when expressed in a unit of mass.

$= 1.2 \text{ J/L/}^\circ\text{C}$ when expressed in a unit of volume (about 1000 less than that expressed in a unit of mass)

For example,

- A mixture of N_2O and O_2 when issuing from a pre-mixed gas cylinder may have a temperature of -60°C . After passing along a rubber tubing of 1 meter length, the temperature of the gaseous mixture may reach 20°C (room temperature).

- On smoking a cigarette, the temperature of the burning tobacco at the end of the cigarette is very high. When air is drawn over this burning end during smoking, its very high temperature falls dramatically by the time it reaches the mouth. At the same time, the quantity of heat lost to the environment is very small.

- The heat required to warm up inspired air is very small because air has a very low specific heat. When a patient breathes cold air (10°C) at a rate of 6 liter/min, the air is warmed up through the trachea to 34°C .

The quantity of heat needed to warm up the inspired air $= \text{flow} \times \text{specific heat} \times \text{temperature rise}$.

$$= 6 \text{ L/min} \times 1.2 \text{ J/L} \times (34-10)^\circ\text{C}$$

$$= 172.8 \text{ J/min}$$

$$= 2.88 \text{ Watt (as } 1 \text{ Watt} = 1 \text{ J/s)}$$

2.88 W is a very small amount of heat loss when compared to the heat lost during basal metabolic rate which is 80 W. Therefore, heat loss during warming cold inspired air is very small.

Latent Heat

Definition:

Latent Heat is defined as the amount of heat required to produce a change of the state of a given substance from one phase to another at a constant temperature.

Normally, the addition or loss of heat is accompanied by a change of temperature, but during the change of the state of a substance, the temperature remains constant.

The term latent is used as this heat used to change the state of a substance is not apparent as no change in the temperature occurs.

Specific Latent Heat is defined as the amount of heat required to convert 1 kilogram of a substance from one phase to another at a given temperature. SI unit of specific latent heat is J/kg.

Types of Latent Heat:

1- Latent Heat of Melting or Fusion:

It is the amount of heat required to change the substance from a solid to a liquid phase without a change in temperature.

2- Latent Heat of Crystallization:

It is the amount of heat given out to change the substance from a liquid to a solid phase without a change in temperature.

3- Latent Heat of Condensation:

It is the amount of heat given out to change the substance from vapor to a liquid phase without a change in temperature.

4- Latent Heat of Vaporization:

It is the amount of heat required to change the substance from a liquid to vapor phase without a change in temperature (figure 5-41).

The amount of latent heat of vaporization is affected by temperature. The lower the temperature, the more the latent heat needed. Therefore, the temperature at which the process of vaporization occurs must be specified.

For example, the latent heat of vaporization when 1 kg of water is converted to 1 kg of vapor (steam) is as follows:

- 2.43 mega J/kg or 583.2 kcal at 20 °C i.e., at room temperature
- 2.42 mega J/kg or 580.8 kcal at 37 °C i.e., at body temperature
- 2.26 mega J/kg or 542.4 kcal at 100 °C i.e., at boiling point

As the temperature increases, the latent heat of vaporization decreases. When the temperature reaches the critical temperature i.e., the temperature at which the substance is completely changed to vapor, the latent heat of vaporization will be zero e.g., the latent heat of vaporization of N₂O is zero at 36.5 °C because the critical temperature of N₂O is 36.5 °C.

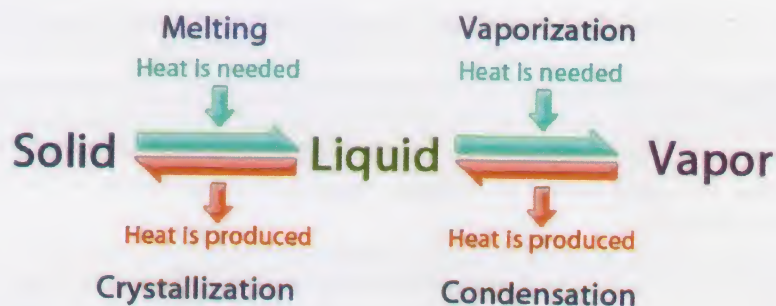


Figure 5-41: Latent heat

Clinical Applications:

1- During the use of ethyl chloride as a local anesthetic: It is stored as a liquid under pressure. When ethyl chloride is sprayed over the tissue, it vaporizes. The latent heat required for the vaporization process is taken from the tissues. Therefore, the tissues and nerves cool down resulting in impairment of nerve conduction and local anesthesia e.g., for opening of skin abscess.

2- During vaporization of volatile anesthetics, latent heat is required, which is obtained from the volatile liquid and the walls of the vaporizer. So, the temperature of the volatile liquid and the vaporizer falls resulting in a decrease in the vaporization. Therefore, heat compensated vaporizers have been developed (see later).

3- During rapid exit of N_2O from its cylinder: N_2O is stored inside the cylinder in a liquid form. When it is vaporized from the cylinder to the outside, latent heat of vaporization is required which is obtained from the walls of the cylinder and the pressure gauge resulting in frost formation on the pressure gauge.

4- During humidification of inspired air; about 34 mg of water vapor are added to each liter of inspired air. This water vapor is obtained from the respiratory mucosa.

For example, when a patient breathes 6 liters/minute, the total latent heat required for vaporization is calculated as follows;

As 34 mg of water vapor are added to each liter,

the total amount of water vapor = $34 \text{ mg} \times 6 \text{ liters/min} = 204 \text{ mg/min}$

the total latent heat needed = specific latent heat of vaporization at $37^\circ\text{C} \times \text{total water}$

$$= 2.42 \text{ mega J/kg} \times 0.000204 \text{ kg/min}$$

$$= 493.68 \text{ J/min} = 8.228 \text{ J/s} = 8.228 \text{ Watt}$$

As specific heat capacity to warm cold inspired air at $10^\circ\text{C} = 2.88 \text{ Watt}$,

total heat loss from respiration at $10^\circ\text{C} = 8.228 + 2.88 = 11.108 \text{ Watt}$

The total heat loss from respiration represents about 13.8 % of the total basal heat loss which is 80 Watt.

Therefore, during anesthesia, humidification of the inspired gases is very important to avoid hypothermia which is more important than warming of the inspired gases.

Thermal Expansion of Solids and Liquids:

When a solid or liquid substance gains heat and its temperature rises, it expands with an increase in its length and volume.

- Coefficient of linear expansion: is the mean increase in the unit length of an object for each 1°C rise.
- Coefficient of volume expansion: is the mean increase in the unit volume of an object for each 1°C rise.

Practical Applications:

When two different substances are attached together and exposed to the same temperature, they will increase in their dimensions by two different degrees. Therefore, the shape of the two attached substances will be changed and curved. This change will be recorded and used in different devices e.g.,

- Bimetallic automatic thermostats.
- Bimetallic thermometers.
- Bimetallic thermo-compensators in Tec vaporizers.

Heat Production and Loss in Human Body

Heat Production in Human Body:

In an average man under resting conditions, the amount of heat produced is:

50 watt/meter² body surface area

or 80 watt total

Heat is produced by:

1- The basal metabolic rate:

It is the minimal amount of heat produced by a fasting healthy individual who is physically and mentally at rest, at room temperature ($20-25^\circ\text{C}$). It depends on age, sex, and surface area of the individual. The

basal metabolic rate of an average woman = $36.5 \text{ kcal/m}^2/\text{hour}$,

and of an average male = $39.5 \text{ kcal/m}^2/\text{hour}$.

N.B: The average surface area of a woman = 1.6 m^2 and of a man = 1.8 m^2

2- Ignition of food:

- Ignition of 1 gram of fat produces 9.5 kcal in vitro and 9.3 kcal in vivo.
- Ignition of 1 gram of protein produces 5.3 kcal in vitro and 4.1 kcal in vivo.
- Ignition of 1 gram of carbohydrate produces 4.3 kcal in vitro and 4.1 kcal in vivo.

3- Shivering of muscles.

Heat Loss in Human Body:

There are 4 routes of heat loss and heat transfer from the human body.

N.B.: Respiration is responsible for 10% of heat loss from the body (8% via evaporation and 2% by convection through heating of air).

	Radiation	Convection	Evaporation	Conduction
Percentage of heat loss from the body by this route	40%	30%	20%	Very minimal %
Definition	<ul style="list-style-type: none"> - It is emission of heat from the body in the form of infrared radiation. - A hot object emits infrared radiations which carry energy from the hot object, thus causing it to cool down. If this radiation is absorbed by another object, that object will become hotter without direct contact between the two objects. 	<ul style="list-style-type: none"> - It is the transfer of heat energy by movement of liquid or gas due to change in their density. - The air layer adjacent to the surface of the body is warmed by conduction and, as it is heated, it expands and becomes less dense and so rises. The resulting convection current carries heat away from the subject. 	<ul style="list-style-type: none"> - It is heat loss due to loss of latent heat of vaporization of moisture on the skin's surface. - Heat loss by this route depends on: <ul style="list-style-type: none"> • the water vapor pressure gradient between the skin and the air, • the total surface area of moist skin exposed to the atmosphere, and • sweating. 	<ul style="list-style-type: none"> - It is the direct transfer of heat energy from one molecule to another. - Metals and some crystals are good conductors of heat, but gases as air around the patient, are poor conductors and act as an insulator.
Medium for transmission	It does not need a medium for its transmission therefore, it can occur in vacuum e.g., the sun radiation reaches the earth via the space.	- It needs a moving medium for heat transmission; therefore, it can not occur in vacuum or in solids.	It needs a medium for evaporation.	- It needs a medium for transfer; therefore, it can occur in solids, liquids and gases, but not in vacuum.
Examples	<ul style="list-style-type: none"> • Cold ambient operation room temperature < 24°. • The large surface area of babies. 	<ul style="list-style-type: none"> • A theatre with high air flow rates 	<ul style="list-style-type: none"> • Dry cold anesthetic gas ventilation. • The use of wet packs. • Sweating. • Open body cavity e.g., abdominal surgeries. 	<ul style="list-style-type: none"> • Contact of the patient with a cold object e.g., an infant touching the wall of an incubator.

Therefore, **Methods of Prevention of Hypothermia:**

- 1- Increase ambient temperature and humidity.
- 2- Warm intravenous solutions and irrigating fluids to at least 37°C.
- 3- Enclose exposed viscera in plastic bags.
- 4- Humidify the inspired gases by attaching a heated humidifier or an artificial heat moisture exchanger to the anesthetic circuit.
- 5- Use warm mattress and blanket (more effective on top of the patient).
- 6- Apply plastic wraps and swaddling around the limbs and the head to insulate the patient.
- 7- Use low flow anesthesia.

Part 7: Humidity

Definition:

Humidity is the quantity of water vapor in a gas.

Types of Humidity

Absolute Humidity:

It is the actual amount (mass) of water vapor present in a given volume of gas (e.g., 1 liter of air) at a given temperature and pressure.

The unit of absolute humidity is **mg/liter or g/m³**

Both units are numerically the same i.e., 44 mg/liter = 44 g/m³.

Relative Humidity:

It is the ratio of the actual amount (mass) of water vapor in a given volume of gas to the amount (mass) required to fully saturate that volume of gas at the same temperature and pressure.

Therefore, relative humidity =
$$\frac{\text{Actual mass of water vap or present (M}_p\text{)}}{\text{Mass of water vap or required to saturate (M}_s\text{)}}$$

From the gas laws (see before)

$$n = \frac{PV}{RT}$$

and as $M \propto n$

$$\text{Therefore, relative humidity} = \frac{P_p V}{RT} / \frac{P_s V}{RT}$$

As V, R, and T are constant

$$\text{Therefore, relative humidity} = \frac{\text{Actual vapor pressure (P}_p\text{)}}{\text{Saturated vapor pressure (P}_s\text{)}}$$

Where n = the number of moles

P = the absolute pressure

V = the volume

R = the universal gas constant

T = the absolute temperature

The unit of relative humidity is **percentage (%)**

Humidity is Temperature-Dependent as a rise in the temperature is associated with more water vapor in the gas.

For example, air which is fully saturated at 21 °C will only be about 40% saturated when the air is warmed to 37 °C.

At room temperature (21 °C), fully saturated air contains 18 mg/L

i.e., absolute humidity = 18 mg/L while relative humidity = 100 %

At 37 °C, fully saturated air contains 44 mg/L

i.e., absolute humidity = 44 mg/L, while relative humidity = 100 %

At 37 °C, when the air is warmed and the water content is not changed i.e., the air is not fully saturated, the absolute humidity is still = 18 mg/L, while relative humidity = $18/44 = 0.40 = 40 \%$

Measurement of Humidity (Hygrometers)

1) Regnault's Hygrometers (Dew-Point Hygrometer):

Idea: It consists of a silver tube containing ether. Air is pumped through the ether and the ether evaporates. This evaporation is associated with loss of heat from the ether and the tube (due to latent heat of evaporation). Therefore, the temperature of the ether and the silver tube will decrease. When their temperature falls, small droplets of water will condense on the shiny outer surface of the silver tube (Figure 5-42). The temperature at which condensation or misting occurs is recorded and called the **dew-point (i.e., the temperature at which the ambient air around the tube is fully saturated)**.

By knowing the dew-point and saturated vapor pressure of the gas, both absolute and relative humidity can be estimated.

The absolute humidity can be estimated by special tables or graphs showing the relationship between the saturated vapor pressure and the water content of a gas.

- The relative humidity can be estimated also as follows:

$$\text{Relative humidity} = \frac{\text{Actual vapor pressure}}{\text{SVP at that temperature}} = \frac{\text{SVP at dew-point}}{\text{SVP at ambient temperature}}$$

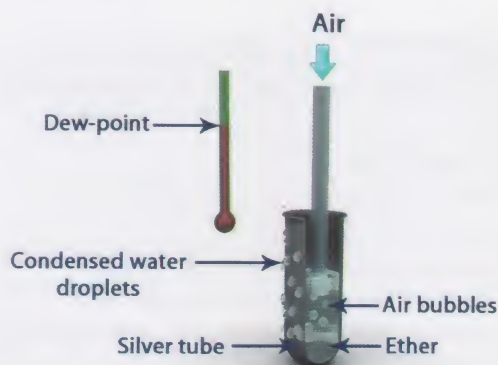


Figure 5-42: Regnault's hygrometer

As the actual vapor pressure at ambient temperature is the same as SVP at dew-point

N.B.: SVP = saturated vapor pressure

2) Humidity Transducers:

Idea: The electrical resistance or the capacitance of a substance changes when the substance absorbs water vapor from the atmosphere (i.e., absolute humidity). This change can be detected by an electronic circuit.

N.B.: A transducer is a device which changes one form of energy to another.

3) Mass Spectrometer

Idea: It is discussed later in the chapter of monitoring during anesthesia. It measures absolute humidity.

4) Weighing:

Idea: There are two methods:

- When a given volume of air is cooled, the water vapor in the air is condensed. The quantity of the condensed water is measured, which equals the absolute humidity.
- When a given volume of air passes in a known weight of concentrated sulphuric acid, silica gel, or anhydrous calcium chloride, the water vapor is absorbed by these substances and the quantity of the water absorbed (i.e., absolute humidity) can be detected by weighing these substances before and after absorption of the water vapor.

5) Hair Hygrometer:

Idea: Human hair increases in length as the relative humidity of the surrounding air increases. One end of hair is attached to a pointer on a humidity scale.

It is accurate in the range of 15-85% relative humidity (figure 5-43).

It is mounted on the wall of the operating room to record the relative humidity.



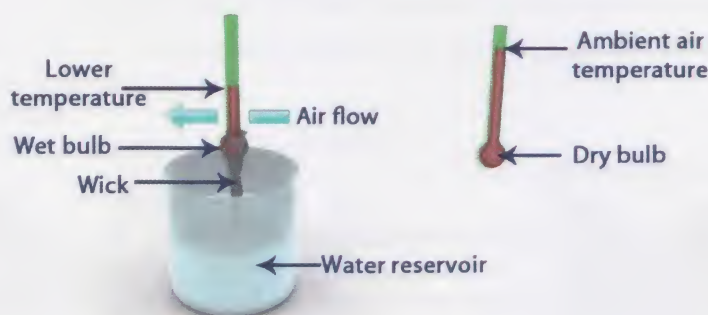
Figure 5-43: A hair hygrometer

Wet and Dry Bulb Hygrometer:

Idea: Two mercury thermometers are mounted side-by-side. One thermometer bulb (the dry bulb) is exposed to the ambient temperature while the other thermometer bulb (the wet bulb) is surrounded by a small wick which dips into a water reservoir. The temperature of the wet bulb depends on the rate of evaporation of the water which in turn depends on the relative humidity of the surrounding air. Due to the loss of the latent heat of vaporization, the evaporation cools the wick, and so, the temperature of the wet bulb is lower than that of the dry bulb. There must be airflow around the wet bulb to prevent a localized increase of humidity which will not be representative of the whole ambient air. Therefore, the difference between the temperatures of the two thermometers can indicate the relative humidity of the ambient air by special tables (figure 5-44).

N.B.:

- Regnault's hygrometers (Dew-point Hygrometers) measure both absolute and relative humidity.
- Humidity transducers, mass spectrometer, and weighing measure absolute humidity.
- Hair hygrometers and wet and dry bulb hygrometers measure relative humidity.



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Figure 5-44: Wet and dry bulb hygrometer

Clinical Applications:

1- Humidification of Inspired Gas:

Normally, humidification and warming of inspired air occur by the nose and upper respiratory tract where the air entering the trachea is almost fully saturated at 34 °C. Its absolute humidity is 34 g/m³ and its relative humidity is 100%.

Bypassing the nose by an endotracheal or a tracheostomy tube allows dry air to enter the trachea. This dry air will be warmed and humidified by the lower inspiratory tract so,

- Water vapor is taken from the **secretions** present in the trachea which then become **dry and tenacious** and **difficult to be coughed** by the patient (a mucous plug may be formed) or **suctioned** by the anesthesiologist.
- Heat is obtained from the surrounding tissues producing **hypothermia**. Vaporization of 1 gram of water removes about 0.6 kcal of heat.

- **Damage of the cilia** occurs by the dry gas.

Therefore, humidification of inspired gas is essential especially in case of:

- Prolonged anesthesia with high fresh gas flow for pediatric or geriatric patients.
- Mechanically ventilated patients in the intensive care unit.
- Infant incubators.

2- Humidification of Operating Rooms:

It is recommended to keep operation rooms' relative humidity **more than 50% (it is usually 60%)**. It is important to **dissipate the static electricity**, thus decreasing the risk of explosion. A higher level causes discomfort to the operation room personnel.

3- Humidification of the Environment around the Body:

It is important to decrease heat loss from the body e.g., in widespread burns or infant incubators.

Methods of Humidification

- Humidification is done by either:
- humidifying the environment or
 - humidifying the inspired gases.

Types of Humidifiers

A) Passive Humidifiers: They conserve heat and water vapor.

Condenser Humidifier (Heat and Moisture Exchanger; HME) (Artificial Nose):

Idea:

- It is a passive humidifier as it does not add water vapor (or heat) to the inspired gases, but it conserves those coming out from the patients.
- It contains a disposable element of rolled corrugated paper, sponge, foam, or fiber material impregnated with a hygroscopic substance such as calcium chloride, lithium chloride, or silica gel.
- During expiration, the warm humidified gas is trapped by the hygroscopic material, where the gas is cooled, and water condenses as the material is warmed. During inspiration the reverse occurs where the moisture evaporates, humidifying the inspired gas (figure 5-45).

Efficacy: is about 70%. It depends on:

- The ambient temperature; as in hot ambient climate the temperature difference between the patient's temperature and the hygroscopic material is minimal, so the evaporation and condensation will be minimal also.
- The minute volumes; as at high minute volumes, the HME is less efficient.

Advantages:

- Cheap.
- Light.
- Easy to use.
- No over-hydration or over-heating.

Disadvantages:

- They increase the apparatus dead space (more than 60 mL³) which can cause significant rebreathing in pediatric patients.
- They increase breathing-circuit resistance and the work of breathing during spontaneous respiration.
- They may be obstructed by excessive water or secretions.
- They increase the risk of infection as the patient may cough into them.

N.B.: Heat and Moisture Exchanger Filters (HMEF):

They are a variant of HME. They act also as effective filters that may protect the breathing circuit and anesthesia machine from bacterial or viral cross-contamination. They are very important on ventilating patients with respiratory infections or compromised immune systems.

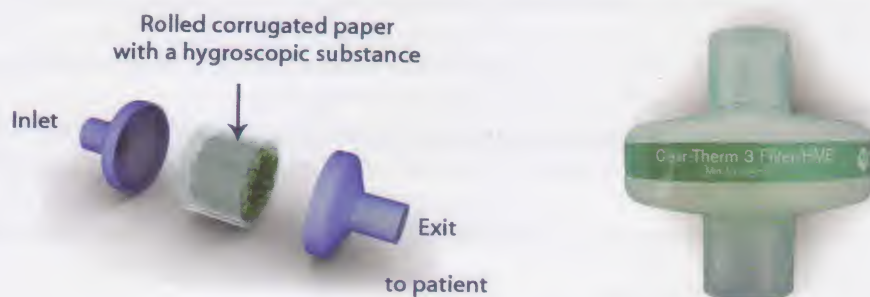


Figure 5-45: A condenser humidifier

B) Active Humidifiers:

They add water vapor (humidifiers) or droplets (nebulizers) to inspired gases.

1- Direct Instillation of Water:

Idea:

Instillation of water droplets directly into the trachea is done. It is not recommended nowadays.

Efficacy: The least efficient method.

Advantages:

- It is the simplest method.

Disadvantages:

- It is the least efficient.
- Rapid and excessive instillation of water into the trachea may cause aspiration syndrome.

3. Heated Water (Hot Water Bath) Humidifiers:

Idea:

A water bath is present through which the dry gas passes. Because increasing temperature increases the capacity of the gas to hold water vapor, and evaporation of water causes loss of heat from the water bath due to latent heat of vaporization (causing cooling of the water and decreasing humidification). Heated humidifiers with a thermostatically controlled electric heater are the most effective. The humidifiers are usually heated to 40-45 °C, but higher temperatures up to 60 °C may be needed to prevent the growth of bacteria within the humidifier.

Efficacy: they are efficient (about 80%).

Types: according to the method of contact between the heated water and the dry gas:

a- Passover Humidifier:

The dry gas passes over a relatively large surface area of heated water in a water chamber.

b- Wick Humidifier:

The dry gas passes through a saturated wick.

c- Bubble-through Humidifier:

The dry gas is bubbled through heated water either by:

- a sintered glass with tiny holes
- or • a perforated screen with tiny holes at the bottom of a wide tube (**Cascade humidifier**) which causes a foam of water and gas.

d- Vapor-phase Humidifier:

The dry gas is mixed with vaporized water (figure 5-46).

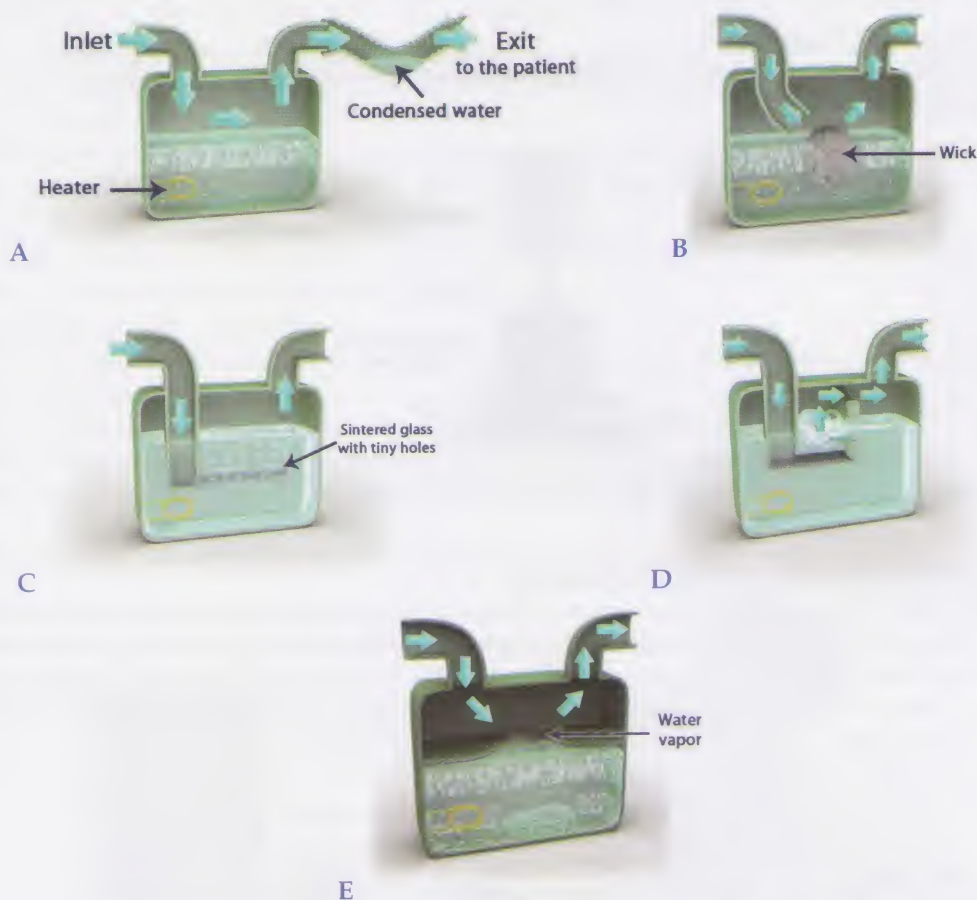


Figure 5-46: Hot bath humidifiers; passover (A), wick (B), bubble-through (C), cascade (D), and vapor (E) humidifiers

Advantages:

They can saturate inspired gases with water vapor at body temperature; therefore, they are used in the intensive care unit and during anesthesia.

Disadvantages:

- 1- They are bulky, and costly.

- 2- There is a risk of **thermal injury of the trachea and lung** due to the use of high temperature. Therefore,
 - a thermostat (a thermistor) is attached to the heater to prevent overheating
 - a thermometer is attached to the humidifier to monitor its temperature
 - another thermometer is present at the patient's end of the delivery tube of the humidifier to monitor inhaled gas temperature.
- 3- **Hyperthermia** may occur especially in pediatric patients.
- 4- **Condensation of the water** at the redundant loop of the inspiration limb of the circuit may obstruct the gas flow to the patient; therefore, a water trap is inserted at the inspiration limb of the circuit.
- 5- There is a risk of **nosocomial infection** due to contamination of the water of the humidifier; therefore, the temperature of the heated water in the humidifier might be increased to 60 °C.
- 6- They do not filter respiratory gases.

3- Heated Element Humidifiers:

Idea: water is vaporized by dripping it on an electrically heated element up to 100-250 °C (figure 5-47).

Efficacy: as heated water humidifiers.

Advantages:

- There is no risk of infection as the high temperature ensures sterility.

Disadvantages

- 1- There is a risk of **thermal injury to the trachea and lung** due to the use of a high temperature; therefore,
 - a thermostat (a thermistor) is attached to the heater to prevent overheating
 - a thermometer is attached to the humidifier to monitor its temperature
 - an other thermometer is present at the patient's end of the delivery tube of the humidifier to monitor inhaled gas temperature.
- 2- It is **not suitable for the use with anesthetic vapors or volatile agents** as the high heat may cause chemical changes to the drugs.



Figure 5-47: A heated element humidifier

4- Nebulizers (Aerosols or Atomizers):

a) Gas-Driven (Pneumatic or Jet) Nebulizer:

Idea: It depends on a Venturi system (the Bernoulli Effect) where the high-speed flow of gas causes a drop in pressure at the end of a capillary tube, immersed in a water reservoir, thus allowing water to be drawn up and entrained from the tube. The entrained water is then broken up into small droplets (5-30 μm) when it hits an anvil. A heater is present to compensate for the loss of heat due to the latent heat of vaporization (figure 5-48).

Efficacy: It is more efficient than heated water humidifiers.

Advantages: It produces humidity as that normally present in the upper trachea.



Figure 5-48: A gas-driven nebulizer

Disadvantages: The entrainment ratio is affected by the back pressure e.g., that of the ventilator; therefore, the efficiency of the device is affected.

b) Ultrasonic Nebulizer:

Idea: The water is dropped on a vibrating surface, or the water is present in a bath with the vibrating surface present within. The frequency of the vibrating surface is about 2 mega Hz. It produces very small droplets (figure 5-49).

Efficacy: It is the most efficient (about 100%).

Advantages:

- The size of the water droplets can be adjusted according to the frequency of the vibrating surface. Therefore, it can produce 1 micron droplets which is the ideal size (see later) for:
 - humidification of the inspired air.
 - administration of inhaled drugs such as bronchodilators and antibiotics.



Figure 5-49: An ultrasonic nebulizer

Disadvantages:

- It is expensive.
- It may be over-efficient, so it may produce a relative humidity of over 100% i.e., super-saturation of the inspired gas; therefore, overloading with water is possible, especially in children, which may cause pulmonary edema.
- The inspired droplets increase the density of the gases and raise the resistance to turbulent flow.
- As the small droplets are stable, they can travel for long distances. If these droplets are infected, cross-infection is very likely to occur.

N.B.: The risk of infection can occur by all types of humidifiers and nebulizers. Therefore, solutions in the humidifiers must be sterile and frequently changed.

N.B. The Size of the Droplets:

- Droplets $> 20 \mu\text{m}$ are a nuisance as they fall out to form **pools** of water either in the **tubing** or in the **upper respiratory tract**.
- Droplets of $5-10 \mu\text{m}$ fall out in the region of the **pharynx**, **larynx**, and **trachea**.
- Droplets of $2-5 \mu\text{m}$ are optimal for tracheobronchial deposition to **loosen secretions**.
- Droplets of $0.5-2 \mu\text{m}$ ($1 \mu\text{m}$) pass through the bronchial tree to be deposited in the **alveoli** (the ideal size).
- Droplets $< 0.5 \mu\text{m}$ are **extremely stable** and can be inspired and then expired again (figure 5-50).

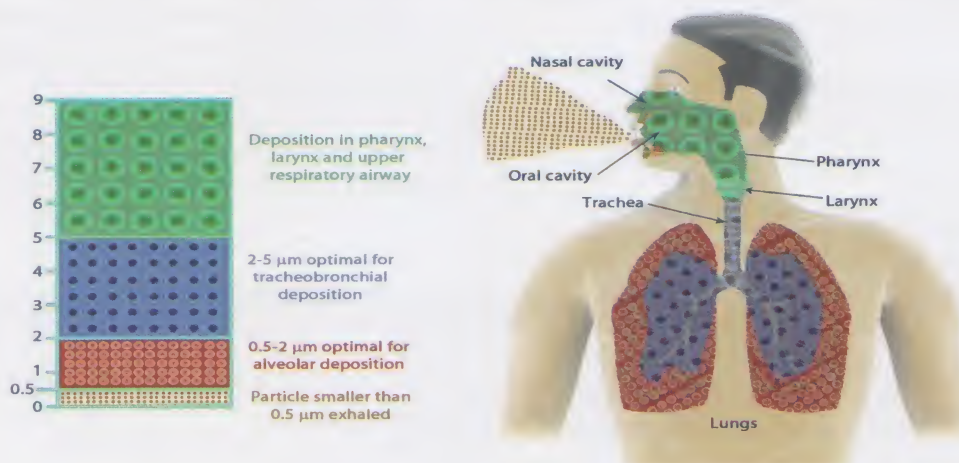


Figure 5-50: Droplet sizes and their deposition in the lungs

Part 8: Flow of Fluids

Definition of Flow (F)

It is the quantity (Q), "volume or mass" of fluid i.e., a gas or liquid, passing across a point in unit time (t).

$$F = \frac{Q}{t}$$

Therefore, the flow is the rate of the change of quantity which has a symbol (\dot{Q}). It is pronounced "Q dot". The small dot above the letter Q indicates the rate of change of quantity to differentiate the flow from the quantity (Q).

Flow of Fluids may occur through:

- A) A tube of a constant diameter.
- B) A tube of a variable (non-uniform) diameter.
- C) An orifice.

A) Flow of Fluids through a Tube of a Constant Diameter

In order to drive a fluid through a tube, a pressure difference (ΔP) must be present across both ends of the tube i.e., P1-P2.

Laminar Flow	Turbulent Flow
<p>Characteristics:</p> <ul style="list-style-type: none"> • It occurs when a flow passes through a smooth uniform tube. • The fluid moves in a steady regular manner and there are no eddies (figure 5-51). The fluid passes as if it is in concentric layers which are parallel to the sides of the tube. The flow is greatest in the central axial layer (twice the mean flow) and decreases gradually towards the periphery where it reaches zero in the layer touching the sides of the tube i.e., parabolic velocity profile. • The flow is silent. • It occurs when the flow moves with a velocity below a critical velocity. • The resistance is lower than that for the same turbulent flow. • The flow of fluids varies directly with the pressure difference (ΔP) i.e., the relationship between the flow and the pressure is linear (figure 5-52) and the resistance (R) is constant. <p>Factors affecting the laminar flow: These factors determine the Hagen-Poiseuille formula.</p> <p>As $\dot{Q} = \Delta P / R$</p> <p>The resistance (R) is affected by:</p> <ol style="list-style-type: none"> 1- Viscosity of fluid (η): the resistance is directly proportionate to the viscosity i.e., $R \propto \eta$ 2- Length of the tube (L): the resistance is directly proportionate to the length i.e., $R \propto L$ 3- Radius of the tube (r): the resistance is inversely proportionate to the power of 4 of the radius i.e., $R \propto 1/r^4$ <p>Therefore, $R \propto \frac{h \times L}{r^4}$</p>	<p>Characteristics:</p> <ul style="list-style-type: none"> • It occurs when a flow passes through a smooth uniform tube with a constriction, an orifice, a sharp bend, or some other irregularity. • The fluid moves in an irregular manner and there are eddies (figure 5-51). The fluid passes in a haphazard manner and the lines of the flow are not parallel to the sides of the tube. There is no marked difference between the velocity in the center and the periphery i.e., flat flow profile. • The flow is noisy i.e., it creates sounds e.g., carotid bruit and cardiac murmurs. • It occurs when the flow moves with a velocity above a critical velocity. • The resistance is higher than that for the same laminar flow. • The flow is not directly proportional to the pressure difference (ΔP), but ΔP is proportional to the square of the flow i.e., the relationship between the flow and the pressure is not linear (figure 5-52) and the resistance is not constant. <p>Factors affecting the turbulent flow:</p> <p>a) The onset of turbulent flow occurs when the Reynolds number is > 2000</p> <p>Reynolds number = $\frac{\text{velocity} \times \text{density} \times \text{radius}}{\text{Viscosity}}$</p> $= \frac{v \times \rho \times r}{\eta}$ <p>N.B.: Critical velocity occurs when the Reynolds number is > 2000</p> <p>If the Reynolds number is < 2000, laminar flow occurs.</p> <p>b) The turbulent flow is affected by;</p> <p>$Q \propto \sqrt{\text{pressure}}$ $P \propto \quad^2$</p>

But as $\dot{Q} = \Delta P / R$

Therefore, $\dot{Q} = \frac{DP \times r^4}{h \times \pi}$

When a **proportionality constant** value for the cross sectional area ($\pi/8$) is included in the formula, **Hagen-Poiseuille Formula or Equation** is produced

$$\dot{Q} = \frac{DP \times r^4 \times P}{h \times L \times 8}$$

i.e., laminar flow obeys **Hagen-Poiseuille formula** and depends on **the viscosity**.

$\dot{Q} \propto 1/\sqrt{\text{length}}$

$P \propto \text{length}$

$\dot{Q} \propto 1/\sqrt{\text{density}}$

$P \propto \text{density}$

$\dot{Q} \propto r^4$

Therefore,

$\dot{Q} \propto \sqrt{\text{pressure}} \times r^4 / \text{density} \times \text{length}$

i.e., turbulent flow does not obey **Hagen-Poiseuille formula** and depends on **the density**.

Clinical Applications:

1- To increase the rate of transfusion of fluids through an intravenous line, it is more important to increase the radius of the cannula inserted rather than to increase the pressure, as flow is proportional to pressure i.e., an increase in the pressure increases the flow by the same ratio, but the flow is proportional to the power of 4 of the radius i.e., an increase in the radius produces an increase in the flow by 16 times (if $r = 2$ so, $2^4 = 16$).

2- Resistance to breathing is much greater when a tracheal tube of a small diameter is used as in pediatrics

3- To determine the peripheral vascular resistance

As $\dot{Q} = \Delta P / R$ or $P = \dot{Q} \times R$

This relationship can be applied to the circulation as

Mean blood pressure (P) = Cardiac output (\dot{Q}) x Resistance (R)

Clinical Applications:

1- During bronchial asthma, broncho-constriction occurs; therefore, the velocity of flow is increased above the critical velocity and the flow becomes turbulent where the resistance is very high. When **helium** is used (it has **very low density**) with oxygen, the density of the inhaled flow is decreased; therefore, the Reynolds number falls below 2000 and the flow returns back to the laminar flow with a low resistance.

2- Flow of air in the respiratory tract is a mix between laminar and turbulent flow.

- In the wider parts as the nose, nasopharynx, and trachea, the flow is more laminar.
- In the branches of the bronchial tree, the flow is more turbulent.
- In the lower respiratory tract as the surface area is large, the velocity is low so the flow is more laminar again.

Any pathology as spasm or infection increases the turbulent flow.

3- During anesthesia, reduction of the resistance to flow can be achieved by **avoiding the angle piece connector** and **making the internal surface of the breathing circuit smooth**.

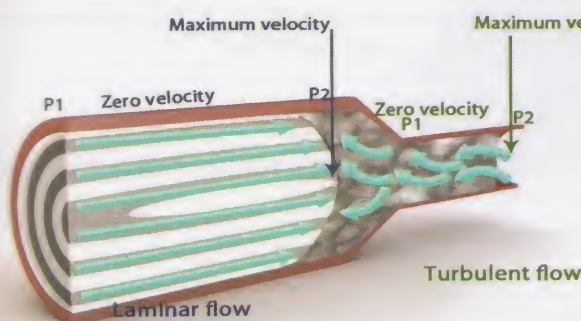


Figure 5-51: Laminar and turbulent flow

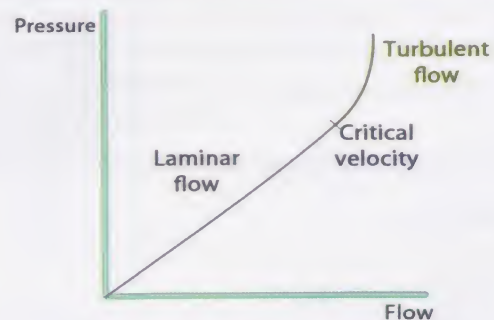


Figure 5-52: The relationship between pressure and flow in laminar and turbulent flow

B) Flow of Fluids through a Tube of a Variable Diameter

Bernoulli Effect:

When a fluid passes through a constriction in a tube, the velocity of the fluid increases and the pressure exerted on the wall of the tube falls. This is named after its discoverer Bernoulli.

Explanation:

There are two types of energy when a fluid passes through a tube:

1- **Potential energy:** associated with the pressure exerted by the fluid on the wall of the tube.

2- Kinetic energy: associated with the velocity of the flowing fluid.

Both potential and kinetic energies are constant.

When a fluid passes through a constriction in a tube, the velocity of the fluid increases, which is associated with an increase in the kinetic energy. As the total energy is constant; therefore, an increase in the kinetic energy is accompanied by a fall in the potential energy which is associated with a decrease in the pressure exerted on the wall of the tube. The pressure exerted on the wall at the site of the constriction may fall greatly to be sub-atmospheric.

Venturi Arrangement:

When a cross-sectional area of a tube gradually decreases towards a constriction then gradually increases again, this is called a Venturi tube (figure 5-53).

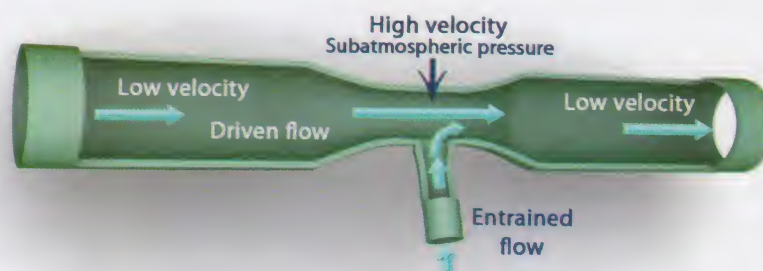


Figure 5-53: A Venturi injector

The fluid passing through a Venturi shows the following changes:

- At first the velocity increases gradually as the fluid passes through the gradually decreasing cross-sectional area of the tube, and at the site of the constriction, sub-atmospheric pressure occurs (**Bernoulli effect**).
- Then when the fluid passes through the gradually increasing cross-sectional area of the tube, its velocity decreases and the pressure increases gradually again until it reaches its original value.

The Injector:

It is a gas-driven device. Its action is based on Bernoulli and Venturi effects.

At the site of constriction of a tube (sometimes called **jet**) where the potential energy is minimal and the pressure on the wall is sub-atmospheric, if a hole is present, entrainment of a gas or a fluid from the side tube to the main stream flow will occur. The flow through the main stream tube is called the **driving flow** while that passing through the entrainment (side) tube is called the **entrained flow**.

$$\text{Entrainment ratio} = \frac{\text{Entrained flow}}{\text{Driven flow}}$$

For example, if the entrainment ratio = $\frac{8}{1} = 8$, this means that 8 liters/min are entrained by a driven gas of 1 liter/min.

Clinical Applications:

1- **Suction devices.**

2- **Nebulizers:** the driven gas passes through the central tube, and the liquid (an inhaled drug) is entrained via the side tube where it is broken up into small droplets by a disc or an anvil.

Gas-driven (pneumatic or jet) nebulizer is used for humidification of inspired air.

3- **Venturi facemask** for oxygen therapy. The sum of the driven gas (100% oxygen) and the entrained air exceeds the peak inspiratory flow rate; therefore, a constant oxygen percentage is delivered to the patient.

Nasal cannulas and simple oxygen facemasks use also the same idea to entrain air via the nostrils (in the nasal cannulas), or the side holes (in the simple facemask), but the sum of the driven gas (100% oxygen) and the entrained air is below the peak inspiratory flow rate. Therefore, the oxygen % is affected by the patient's respiration, and a variable oxygen % is delivered to the patient.

4- **Jet ventilation** e.g., Sander's injector during bronchoscopy.

Coanda Effect:

Based on the Bernoulli and Venturi effects, when a gas passes through a constriction, a sub-atmospheric pressure is produced. If there are no holes at the site of constriction, the sub-atmospheric pressure will hold the stream along the wall of the wide tube. If a narrow tube is connected to a Y-connection of a wider bore i.e., a tube with two Venturis, the flow which is held to the wall will tend to cling to one side of the Y-connection (i.e., the flow does not divide evenly between the two sides, but flows through only one limb of the 'Y'). This is called the Coanda effect (figure 5-54).

Clinical Applications:

1- The Coanda effect explains:

- the uneven distribution of gas flow to alveoli when there is a slight narrowing of the bronchiole before it divides, resulting in **alveolar collapse**.
- and • the uneven distribution of coronary blood when there is a slight narrowing of the coronary artery before it branches, resulting in **myocardial ischemia**.

2- If a small tube is inserted perpendicularly at the exit of a narrow tube and little pressure is applied, a **simple valve switch mechanism** is produced where the flow can be directed from one exit tube to the other (without any mechanical parts). This device is called **fluidic logic** and can be used in gas-driven ventilators (called **fluidic ventilators**).

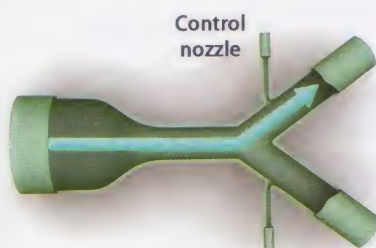


Figure 5-54: The Coanda effect

Q Flow of Fluid through an Orifice

In an orifice, the diameter of fluid (D1) pathway exceeds the length (L1), but in the tube, the length (L2) exceeds the diameter (D2) (figure 5-55). The flow through an orifice is turbulent.

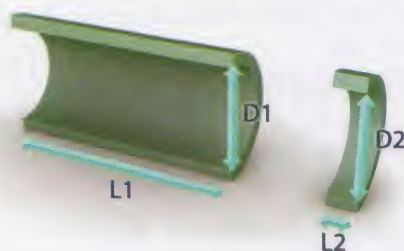


Figure 5-55: A tube (left) and an orifice (right)

Factors Affecting Flow of Fluid through an Orifice:

- 1- The square root of the pressure difference across the orifice i.e., $\dot{Q} \propto \sqrt{P_1 - P_2}$
- 2- The square of the diameter of the orifice i.e., $\dot{Q} \propto \text{diameter}^2$.
- 3- The density of the fluid i.e., $\dot{Q} \propto 1/\text{density}$

Clinical Application:

In the bobbin flowmeter "Rotameter®", at low flow rates, the narrow annular space between the bobbin and the wall mimics a tube. At high flow rates, the width of the annulus is large in relation to the height of the bobbin and the annular space forms an orifice. Thus at low rates, the viscosity of gas determines the position of the bobbin (as it is laminar flow), whereas at higher rates the effect of the density of the gas becomes more important (as it is turbulent flow). It is discussed in more details later in the chapter of "Anesthetic Apparatus & Equipment".

PART 9: FLOW AND VOLUME MEASUREMENTS

Flow and volume measurements include:

- a- Gas flow measurement.
- b- Gas volume measurement.
- c- Liquid flow measurement.
- d- Liquid volume measurement.

GAS FLOW MEASUREMENT (FLOWMETERS)

Includes:

Volume/time methods

I- Methods of Pressure Drop Across an Orifice:

A) Variable Orifice (Constant or Fixed Pressure Drop) Flowmeters:

- 1- Bobbin flowmeter "Rotameter®" or ball flowmeter.
- 2- Wright peak flowmeter (Wright respirometer).

Other Variable Orifice Flowmeters

- 1- Ewing flowmeter.
- 2- Coxeter flowmeter.
- 3- Heidbrink flowmeter.

B) Constant or Fixed Orifice (Variable Pressure) Flowmeters:

- 1- Water depression flowmeter.
- 2- Bourdon gauge flowmeter.
- 3- Aneroid gauge flowmeter.
- 4- Pneumotachograph.
- 5- Venturi Tube Flowmeter.
- 6- Pitot tube flowmeter.

C) Variable Orifice and Pressure Flowmeters:

Water sight flowmeter.

II- Other Flowmeters (Intermittent Flowmeters)

- 1- Hot wire (electric mass or thermistor) flowmeter.
- 2- Ultrasonic flowmeter.

Volume/Time Methods:

Idea: Simply, **flow rate** is calculated from **the volume of gas collected in unit time**. The volume of the gas is collected in a container of a known size.

- In **the anesthetic machine**, if a 2 L reservoir bag is filled with O₂ in 5 seconds, the flow rate will equal $2/5 = 0.4 \text{ L/s}$ or 24 L/min.
- In a **soap film flowmeter**, the gas flow rate is derived from the time taken for a soap film bubble to ascend through a vertical glass tube of known dimensions.

I- Methods of Pressure Drop Across an Orifice:

A) Variable Orifice (Constant or Fixed Pressure Drop) Flowmeters:

1- Bobbin Flowmeter "Rotameter®" or Ball Flowmeter:

.....see later in flowmeters.

2- Wright Peak Flowmeter (Wright Respirometer):

It was invented by Wright & McKerrow 1959 and modified by Wright in 1978.

Idea:

- It is a **vane anemometer**; as when the gas flow passes through the flowmeter, the vane rotates around a central axle within a small cylinder. The walls of the cylinder are perforated with a number of tangential slits which allow the gas to escape. Rotation of the vane is opposed by the force of a coiled spring which drives a pointer around a dial by a set of gears. When the vane rotates due to the flow of the gas, the vane is prevented from returning back to its original position by a ratchet. After the maximum reading is taken, the vane can be released by pressing a bottom and the pointer returns to zero. The vane does not rotate when the direction of the flow is reversed (figure 5-56).

N.B.: The peak flow of a normal adult = 400-500 L/min

The peak flow of an emphysematous patient = < 100 L/min.

- In the electronic versions, rotation of the vane is detected electronically by cutting through a beam of light.....see later.

Advantages:

- It is incorporated in the breathing system, in the expiratory limb, so any leaks in the inspiratory limb are eliminated by evaluation of the expired minute volume.
- It is incorporated as near as possible to the tracheal tube to decrease the effect of system compliance on its function.
- It can be used to measure inspired and expired volumes and flow up to 1000 L/min.

Disadvantages:

- Inaccuracy: It overreads at high tidal volumes and underreads at low tidal volumes due to the inertia and the drag of gears.
- It is affected by moisture which causes the pointer to stick.
- It can not be used to measure both the inspiratory and expiratory flow because it detects the flow in one direction only.
- It is not suitable in measuring a continuous flow.

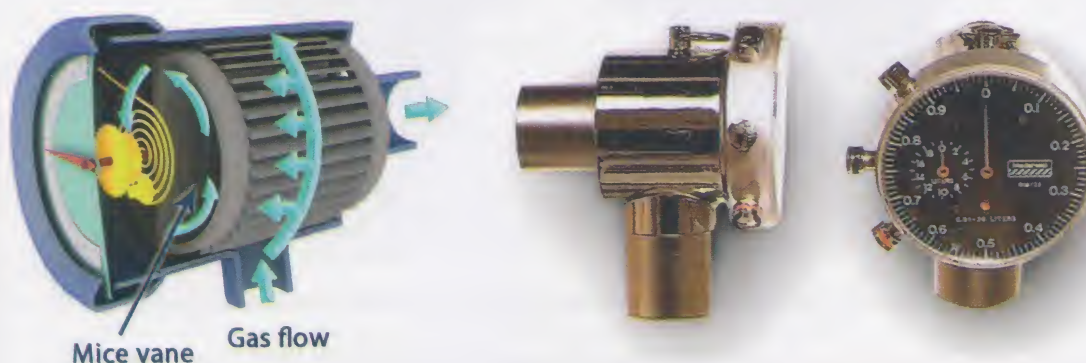


Figure 5-56: Wright peak expiratory flowmeter

Other Variable Orifice Flowmeters

They were used in the past, but now they are only of historical interest.

1- Ewing flowmeter: two balls were used for stability instead of one ball in an inclined tube flowmeter.

2- Coxeter flowmeter: The bobbin was fitted inside a vertical uniform glass tube with a series of holes on the side.

3- Heidbrink flowmeter: a plunger moves inside a conical glass tube where the position of the plunger depends on the balance between the downward pressure exerted by its weight and the pressure drop across the annular orifice (figure 5-57).

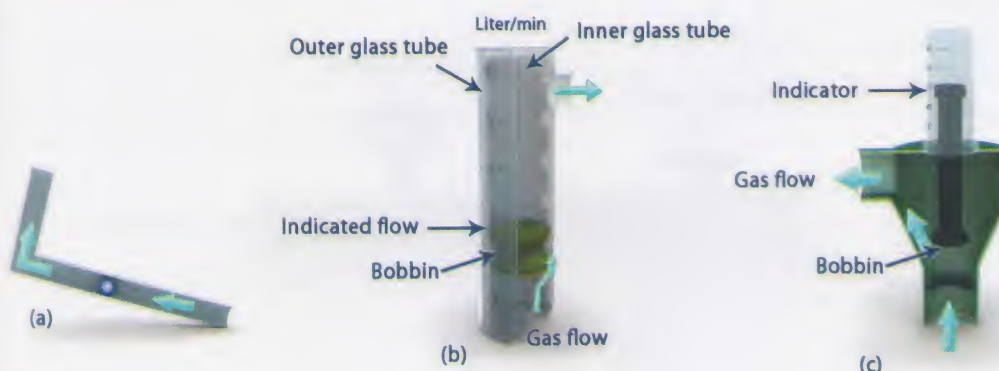


Figure 5-57: Ewing (a), Coxeter (b), and Heidbrink (c) flowmeters

B) Constant or Fixed Orifice (Variable Pressure) Flowmeters:

1- Water Depression Flowmeter:

Idea: The gas flows through a fixed orifice and the pressure drop across the orifice is measured with a colored water manometer. The gas flow rate varies with the pressure drop across the orifice (figure 5-58).

Advantages:

- Simple.

Disadvantages:

1- The flow of the gas through the orifice is turbulent, so the pressure drop across the orifice is proportional to the square of the flow rate. Therefore, the scale is non-linear, being crowded at the lower readings and expanded at the higher readings. This is not suitable in anesthetic practice.

A recent modification of this flowmeter has been done, where the orifice is replaced by a tube, so the flow becomes laminar and consequently the pressure drop across the orifice is proportional to the flow rate and a linear scale is produced.

2- There is a danger of blowing water into the patient's circuit when the cylinders are suddenly opened.

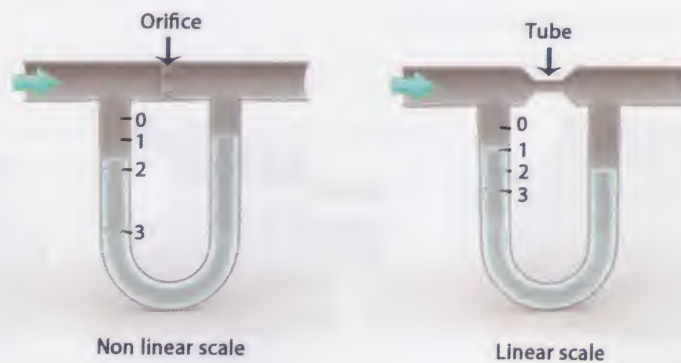


Figure 5-58: Water depression flowmeter; orifice type (left) and tube type (right)

2- Bourdon Gauge Flowmeter: The most common in anesthetic practice.

Idea:

The gas flows through a fixed orifice and the pressure drop across the orifice is measured with a Bourdon gauge. An increase in the flow uncoils the coil of the gauge, where a pointer moves over a scale. The gas flow rate varies with the pressure drop across the orifice (figure 5-59).

Advantages:

- The meter is not affected by changes in position; therefore, it is used to measure the flow through a gas cylinder on transporting patients from one place to another.

Disadvantages:

- 1- The flow of the gas through the orifice is turbulent, so the pressure drop across the orifice is proportional to the square of the flow rate. Therefore, the scale is non-linear.
- 2- It is affected by what is in front of it; therefore, complete occlusion of the outlet will cause the meter to record maximum flow.



Figure 5-59: Bourdon gauge flowmeter

5- Aneroid Gauge Flowmeter:

Idea:

The same as the Bourdon gauge flowmeter but the pressure drop is measured by an aneroid gauge where an increase in the pressure will move a diaphragm, which in turn moves a pointer on a non-linear scale.

5- Pneumotachograph:

Idea:

The gas passes through a laminar resistor. The laminar resistor is either a series of parallel tubes "Fleisch pneumotachograph" or a large diameter gauze screen or mesh "Lilly pneumotachograph" to generate laminar flow even at high flow rates. The parallel tubes or the gauze provide little resistance to the flow, so respiratory airflow from the patient causes a small pressure drop. This pressure change is measured by a transducer, which converts the pressure change into an electrical signal, which in turn can be displayed and recorded (figure 5-60).

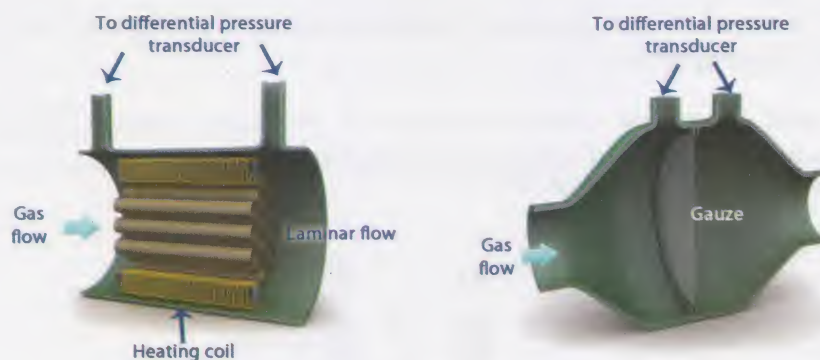


Figure 5-60: Pneumotachograph; parallel tubes (left) or gauze screen (right)

Advantages:

- It can measure rapid changes in the patient's respiration i.e., it can be used as a spirometer.
- It can be used to measure the tidal volume if the time of the flow is recorded.
- It is accurate especially after addition of a heated element (see below).
- It is used to calibrate flowmeters.

Disadvantages:

1- Readings can be affected by:

- A change in the viscosity of the gas, by either a change in the composition or the temperature, as the flow through the device is laminar, e.g., addition of anesthetic gas, may affect the reading and the accuracy.
- Condensation of water vapor inside the laminar resistor may occur, which increases the resistance of the resistor and causes pressure drop. This also may affect the accuracy.

Therefore, to increase the accuracy and solve these problems, a heated coil surrounds the device which maintains the temperature of the device constant.

1- It is used only for intermittent flow (not for continuous flow).

5- Venturi Tube Flowmeter:

Idea:

When the gas passes through a narrowed part of a tube, it accelerates and the flow becomes turbulent. When the velocity increases, some of the potential energy is converted into kinetic energy and the pressure recorded from a side arm in the constricted part of the tube will be less than the pressure in the wider part of the tube (figure 5-61).



Figure 5-61: Venturi tube flowmeter

Disadvantages: Because the flow is turbulent, the pressure difference is roughly proportional to the square of the flow rate and the scale is non-linear. It is affected by the change in gas density.

6- Pitot Tube Flowmeter:

Idea:

A Pitot tube is connected to the fluid in alignment with the direction of the fluid flow where the tube faces the stream of the fluid. The fluid inside the Pitot tube is stationary.

The kinetic energy of the moving fluid is converted to potential energy inside the Pitot tube.

The kinetic energy is proportional to the square of the fluid velocity.

The potential energy is proportional to the pressure in the Pitot tube.

Therefore, an increase in the kinetic energy is accompanied by an increase in the potential energy which in turn is accompanied by increased pressure in the Pitot tube. So, the pressure measured by the Pitot tube that faces the direction of the fluid flow is proportional to the kinetic energy and therefore to the square of the fluid velocity.

The kinetic energy is sensed by the difference in pressure between that inside the Pitot tube and the lateral pressure exerted by the gas (figure 5-62).

Disadvantages:

- Because the kinetic energy, the potential energy and its related pressure inside the Pitot tube is proportional to the square of the fluid velocity; therefore, the scale is nonlinear.
- The device is used in a limited range of flow.

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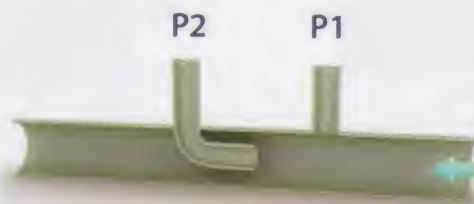


Figure 5-62: Pitot tube flowmeter

C) Variable Orifice and Pressure Flowmeters

Water Sight Flowmeter:

Idea:

Both the pressure drop and the cross-sectional area of the orifices increase as flow increases. The gas passes through a tube which is immersed in water and escapes through one or more hole bored in the side of the tube. The pressure drop across the hole is balanced by the hydrostatic pressure of the external water column.

If flow rate is increased, the pressure drop across the hole is increased and the water in the flowmeter is forced down until the gas escapes through a lower hole. Observation of the lowest hole through which the gas is bubbling, yields a measure of flow rate (figure 5-63).

Disadvantages:

- It can not be used with high flow rates as the resultant excessive bubbling prevents proper observation of the tubes.



Figure 5-63: Water sight flowmeter

II- Other Flowmeters (Intermittent Flowmeters)

1- Hot Wire (Electric Mass or Thermistor) Flowmeter:

Idea:

An electric current passes through a thermistor (a semiconductor device formed of fine platinum wire) which changes its resistance with the change of temperature. The current heats the thermistor, and the gas flow which is to be measured, passes through the thermistor, carrying away heat energy. To maintain the thermistor at a constant temperature, the electric current must be increased if the gas flow increases, because an increased gas flow carries away more heat energy. Therefore, the current required is a measure of the gas flow (figure 5-64).

Disadvantages:

- The temperature of the gas flow can affect the accuracy of measurement because cool gas removes more heat from the thermistor than warm gas, so a false high reading is obtained. Therefore, measurement of the temperature of the gas with a second thermistor is essential before the flow passes over the first thermistor, and a correction factor is needed.
- The measurement of the gas flow rate is also affected by presence of water vapor, gas composition and its thermal conductivity.
- There is an inability to detect reverse flow.
- There is a possibility that the heated wire may be a potential ignition source for fire in the breathing manifold.

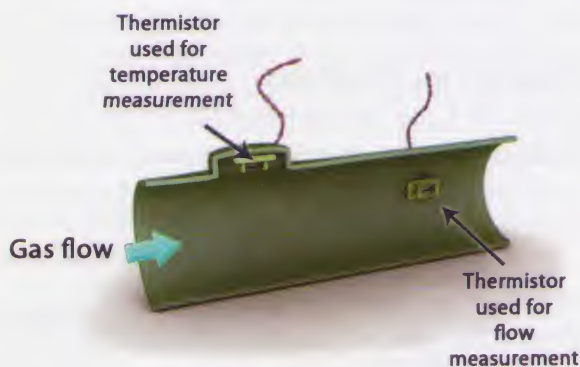


Figure 5-64: Electric mass flowmeter

2- Ultrasonic Flowmeter:

Idea: It is the most common type used nowadays.

The gas flow passes through a tube containing a small vertical rod fixed at right angles to the direction of gas flow. Turbulent eddies and vortices are produced downstream from the rod. The number of eddies is directly related to the flow rate. Eddies are detected by an ultrasonic beam (generated and received by piezoelectric crystals) which is mounted at an angle of 40° to the gas stream (figure 5-65).

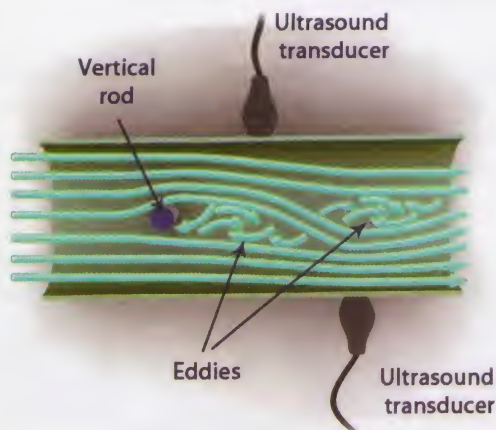


Figure 5-65: Ultrasonic flowmeter

Advantages:

- The device is not affected by temperature, humidity, or gas composition.

Disadvantages:

- The device can not be used for small flow rates below 5 L/min because eddies are not formed.

GAS VOLUME MEASUREMENT (SPIROMETERS OR RESPIROMETERS)

Includes:

A) Direct Measurement of Gas Volume:Wet Spirometer:

Benedict Roth spirometer.

Dry Spirometers:

- 1- Piston dry spirometer.
- 2- Vitalograph (wedge spirometer).
- 3- Dry gas meter.
- 4- Wright respirometer.
- 5- Dräger volumeter.

B) Indirect Measurement of Gas Volume:

- 1- Magnetometers.
- 2- Pneumographs.
- 3- Capacitance spirometry.
- 4- Respiratory inductance plethysmograph (respirace).

A) Direct Measurement of Gas Volume:

These devices need to be connected directly to the patient's airway with leak-free connections.

Wet Spirometers:**Benedict Roth Spirometer:**Idea:

A light rigid bell (cylinder) of 6 liters capacity is suspended inside a larger double walled container. The space between the walls is filled with water to produce a seal and prevent leakage of gas from the bell. This seal is small in volume to decrease the volume of the gas which dissolves in the water. The bell moves with the patient's respiration and this movement is recorded by a pen on a rotating drum (figure 5-66).

It is used to provide a standard for calibration of flowmeters or other volume measuring devices.

Disadvantages:

- It is inaccurate at high respiratory rates or during the performance of a forced vital capacity maneuver because:
 - a large pressure must be generated within the bell to overcome the inertia of the moving parts.
 - the change in pressure produces fluctuations in the water level and compression of gas within the bell, thus causing a lag in the excursion of the pen.

To overcome these problems;

- a light-weight bell of large diameter is used to decrease the acceleration during rapid breathing.
- a large volume of water is used to decrease the oscillations.

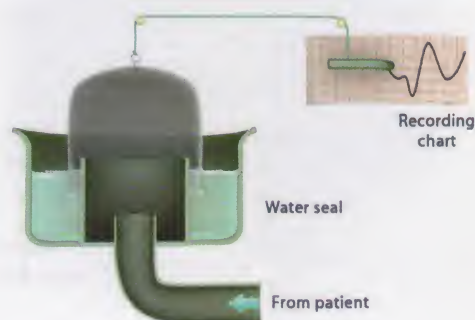


Figure 5-66: Benedict Roth spirometer

Dry Spirometers:

1- Piston Dry Spirometer:

Idea:
It consists of a large diameter, light-weight piston moving horizontally within a cylinder. A low friction seal between the two is achieved with a rolling diaphragm (figure 5-67).

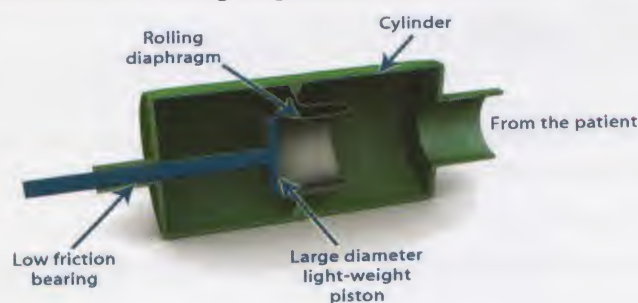


Figure 5-67: Piston dry spirometer

2- Vitalograph (Wedge Spirometer):

Idea:
It consists of a bellows of 6 liters capacity which is used to measure gas volume. The bellows is square in shape and folded. The bottom plate of the bellows is fixed while the top plate of the bellows is pivoted so that the bellows becomes wedge shaped when fully expanded. The motion of the bellows is transferred to a pen which records the volume changes on a chart. The chart is motor driven, which allows expired volume-time graphs to be recorded (figure 5-68).

It is more compact and portable. It is used to assess pulmonary function tests e.g., forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), peak expiratory flow rate (PEFR), and maximum mid-expiratory flow rate (MMEF). It is important to ensure that the patient makes an airtight seal with the mouthpiece and that the nose is occluded with a nose clip.

Disadvantages:

It is inaccurate at high respiratory flow rates.



Figure 5-68: Vitalograph

3- Dry Gas Meter:

Idea:

It consists of a box containing two compartments, A and B. The gas passes into compartment B, compressing the bellows, which simultaneously empties compartment A. As the bellows is compressed, they move a lever to provide a volume recording and also move a rod to shift the valves to a new position. In this position, compartment A is now filled until it also moves the rod and lever mechanism (figure 5-69).

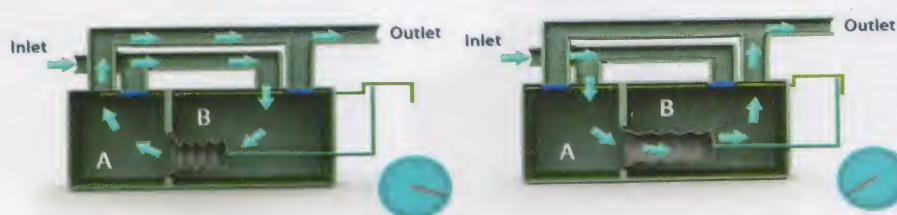


Figure 5-69: Dry gas meter

Advantages: It is portable, accurate, and relatively cheap. It can be used to record larger volumes and high flow rates; therefore, it is used in domestic gas supplies.

4- Wright Respirometer:

Idea:

a) Mechanical Wright Respirometer (Wright Peak Flowmeter):

.....see above.

b) Electronic Wright Respirometer (Electronic Volume Monitor):

It consists of a vane mounted on an axle inside a cylinder through which the gas flows. To create a spiral movement of air, angled blades are present on either side of the moving vane. There are two infrared beams that cross the vane. The beams are interrupted by the vane when it rotates. These beams are sensed and recorded by an electronic processor which can indicate the tidal volume and minute ventilation (figure 5-70).

Advantages:

- The vane can move in both directions; therefore, it can record the gas volume during inspiration and expiration.
- It is more accurate than the mechanical type because the drag of the gears on the vane is eliminated.

Disadvantages:

- It needs a source of electric power.
- It is less portable.
- It is more expensive.

N.B.: In some anesthetic machines, a respirometer is usually incorporated in the expiratory limb near the exhalation valve. Another respirometer may be incorporated in the inspiratory limb. In other anesthetic machines, a bidirectional respirometer is incorporated at the Y connector to record the actual delivered and exhaled tidal volumes.

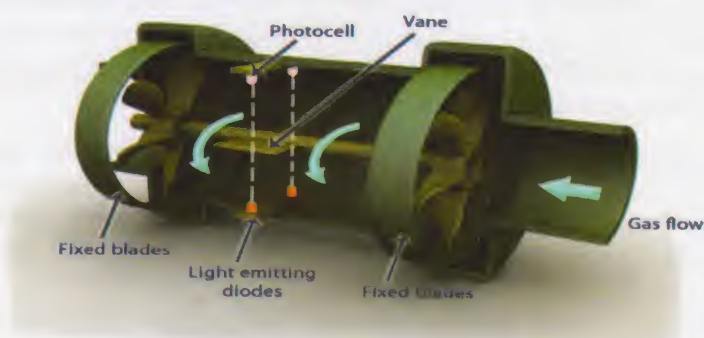


Figure 5-70: Electronic Wright respirometer

5- Dräger Volumeter:

Idea:

It consists of two light, interlocking, dumb-bell-shaped rotors which rotate inside a cylinder. When the gas flows, the rotors rotate and activate a set of gears, which drives a pointer on a calibrated scale (figure 5-71).

Advantages:

- It is accurate.
- It can record the flow in both directions.

Disadvantages:

- It is more expensive.
- It is affected by moisture.

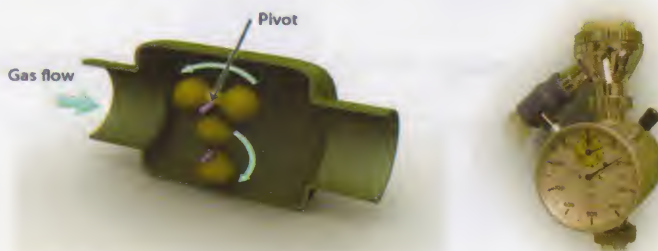


Figure 5-71: Dräger volumeter

8) Indirect Measurement of Gas Volume:

These devices can record the tidal volume by measuring changes in diameters, circumference, or cross-sectional area of the thorax and abdomen.

1- Magnetometers:

Idea:

It is used to measure changes in the diameter of the chest and abdomen in studies of chest wall mechanics. A magnetic field is generated by small electromagnets attached to the chest wall and abdomen and the strength of the magnetic field is sensed by small coils.

Disadvantages: It is inaccurate.

2- Pneumographs:

Idea:

These devices are used to sense changes in chest and abdominal circumference. There are two sensors; one is placed around the chest and the other is placed around the abdomen.

There are many types of sensors:

- A non-elastic tape sensor; the ends of each tape are connected to another sensor which measures the distance between them. The change in the length is related to the change in the volume.
- A small bellows (usually made from corrugated rubber tubing); the interior of which is connected to a pressure transducer (figure 5-72). The change in the pressure is related to the change in the length, which in turn is related to the change in the volume.
- Mercury-in-rubber strain gauge; it consists of a narrow silicon rubber tube containing mercury with electrical contacts at each end. Elongation of the tube narrows and lengthens the mercury column, and so changes the resistance to the passage of an electrical current.
- 4 electrodes applied to the chest that measure electrical impedance when a high frequency oscillating current is passed through the chest wall. It is used in pediatric intensive care units.

Disadvantages:

- They are affected by the change in position, so they need frequent recalibrations.

3- Capacitance Spirometry:

Idea:

Changes in tidal volume can be detected by measuring the change in capacitance between two plates placed in front and behind the subject. It is used for measuring apneic periods in infants.

4- Respiratory Inductance Plethysmograph (Respirace):

Idea:

There are two sensing elements; one over the chest and another one over the abdomen. Each sensing element consists of a wire coil which is sewn into an elastic strap in a zigzag pattern. Expansion of the chest and abdomen increases the space between the coils, and so alters the inductance generated by a high frequency alternating current (a.c.). The change in inductance is directly related to the cross sectional area of the body enclosed by the coil, and so is closely related to the change in volume (figure 5-73).

Disadvantages:

- It is affected by the change in position, but less than indirect devices.

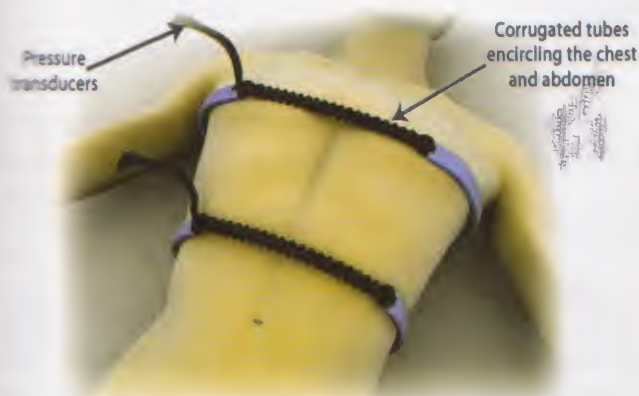


Figure 5-72: Pneumographs

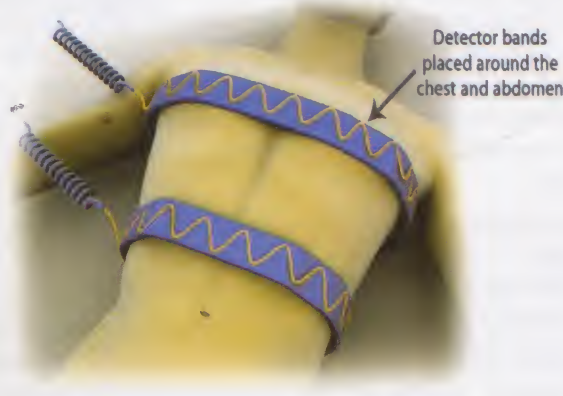


Figure 5-73: Respiratory inductance plethysmograph

LIQUID FLOW MEASUREMENT

Includes:

Measurement of Intravenous Infusion Rate:

- 1- Infusion controllers.
- 2- Infusion pumps.
- 3- Syringe pumps.
- 4- Target controlled infusion system (TCI System), computer-assisted continuous infusion (CACI).
- 5- Variable orifice flowmeters.

Measurement of Blood Flow:

I) Direct methods:

a- Measurement of Mean (Continuous or Steady) Flow:

- 1- Volume/time method.
- 2- Liquid rotameter.
- 3- Potter electro-turbinometer.
- 4- Heat dissipation methods.

b- Measurement of Oscillatory (Pulsatile) Flow:

- 1- Methods based on pressure measurement.
- 2- Electromagnetic flowmeter.
- 3- Ultrasonic flowmeter.
- 4- Thin-film flowmeter.

II) Indirect Methods:

- 1- Fick principle.
- 2- Dilution technique.
- 3- Clearance methods.
- 4- Venous occlusion (limb) plethysmography.
- 5- Physiologically inaccurate methods.

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Measurement of Intravenous Infusion Rate

1- Infusion Controllers:

It is the most common type used in anesthetic practice.

Idea:

The number of drops passing through the fluid chamber (the reservoir) is adjusted by the infusion controller. This number is counted and multiplied by the volume of the single drop. Most infusion sets give drops of 1/15 - 1/20 mL volume for each drop.

The size and the volume of the drop depend on:

1. The surface tension of the liquid: As the drop forms, the surface tension on its surface balances the force of gravity on the liquid in the drop and prevents the drop from detaching from the end of the tube. As the size increases, the weight of the drop eventually becomes too large to be supported by the surface tension and the drop detaches from the end of the tube.
2. The density of the liquid.
3. The size and shape of the tube.
4. The rate at which the liquid is flowing through the tube.

Disadvantages:

Inaccuracy: as both surface tension and density are affected by the temperature and nature of the solution or the blood transfused; therefore, 20% variation in the drop size is expected and so, also in the estimated flow.

2- Infusion Pumps:

Idea:

The number of drops that pass through the fluid chamber is counted by a beam of light or infrared radiations produced by a lamp or a light-emitting diode. The light or infrared radiations pass through the fluid chamber and are detected by a photodetector on the other side of the chamber (figure 5-74). The light intensity falling on the photodetector is reduced every time a drop interrupts the beam. Thus the controller is able to count the drip rate and adjust the flow of liquid by controlling a motorized volumetric pump. Therefore, the volume of the fluid administered and its flow rate are accurately known.

Disadvantages:

The position of the drip counter should be carefully located, otherwise a false count and flow are administered. The light beam should be positioned halfway between the drop-forming orifice and the liquid level. The liquid should occupy one-third of the drip chamber, which should be vertical so that the drops interrupt the light beam correctly.

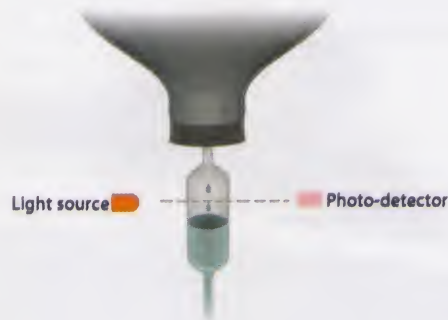


Figure 5-74: Infrared drip counter

5- Syringe Pumps:Idea:

Ordinary syringes, preloaded with the required drug, can be used in a suitable motorized holder. By knowing the exact size of the syringe used and the rate at which the motor pushes the piston of the syringe, the exact rate and volume delivered to the patient are known. The flow in the syringe pump is adjusted by mL/hour. It is an accurate method.

Disadvantages:

- 1- High pressure is developed when the syringe is used, which increases the possibility of extravasation and subcutaneous infusion; therefore,
 - particular care is needed on positioning an intravenous cannula.
 - a pressure alarm and obstruction alarm are needed to be incorporated in the pump to avoid infusion of fluid under high pressure subcutaneously.
- 2- It is only suitable for infusion of small volumes.

4- Target Controlled Infusion System (TCI System)Computer-Assisted Continuous Infusion (CACI):

It is discussed in more details in the chapter "Pharmacology of Anesthesia & Intensive care" (figure 5-75).



Figure 5-75: Syringe pump and TCI system

5- Variable Orifice Flowmeters:Idea:

The same idea as that used in measuring the flow of the gas (see before); for example, flowmeters of renal dialysis or cardiopulmonary bypass equipment.

Measurement of Blood Flow1) Direct Methods:a- Measurement of Mean (Continuous or Steady) Flow:

These methods measure an average flow over a given time.

1- Volume/Time Method:

Idea:

It is the simplest method where the blood is diverted into a graduated vessel for a known time.

Ludwig stromühr (figure 5-76) is used instead to avoid the physiological effects of loss of blood from the circulation.

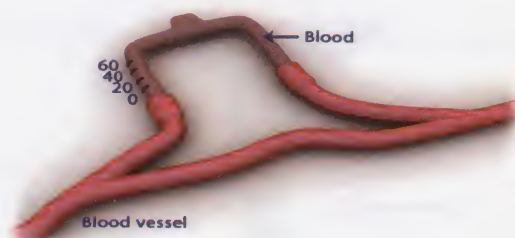


Figure 5-76: Ludwig stromühr

2- Liquid Rotameter:

Idea:

It is similar to the gas rotameter. An increase in flow causes the rotameter to move upwards. This is sensed by the changes of inductance in the coil produced by the movement of the soft iron core attached to the rotameter (figure 5-77).

Disadvantages:

- It may be affected by the viscosity of the blood i.e., hematocrit.

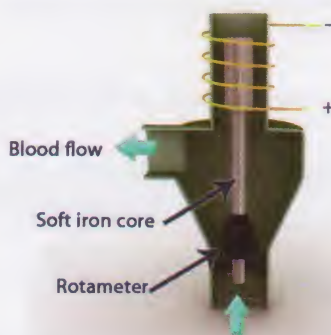


Figure 5-77: Liquid rotameter

3- Potter Electro-Turbinometer:

Idea:

A rotating vane is built around a permanent magnet which is free to rotate in a tube inserted between the cut ends of a blood vessel. The speed of rotation of the rotor is sensed by a pick-up coil situated in the wall of the instrument (figure 5-78).

Disadvantages:

- It does not work at a very low speed of flow due to the high resistance of the flow.

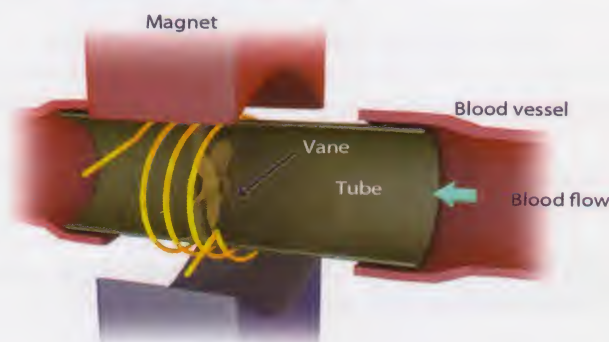


Figure 5-78: Potter turbinometer

4- Heat Dissipation Methods:

Idea:

A heating coil is placed around a blood vessel. When the electrical current passes through the coil, the blood will be heated and the difference of heat between the upstream (with a lower temperature) and downstream thermistor (a higher temperature) is inversely proportional to the blood flow (figure 5-79).

The difference in temperature is either recorded directly by two thermistors or by measuring the change in the resistance of the wire; as the resistance of the wire is proportional to the heat loss.

It can be inserted in the tip of a catheter.

Disadvantages: It is inaccurate when pulsatile flow is present.

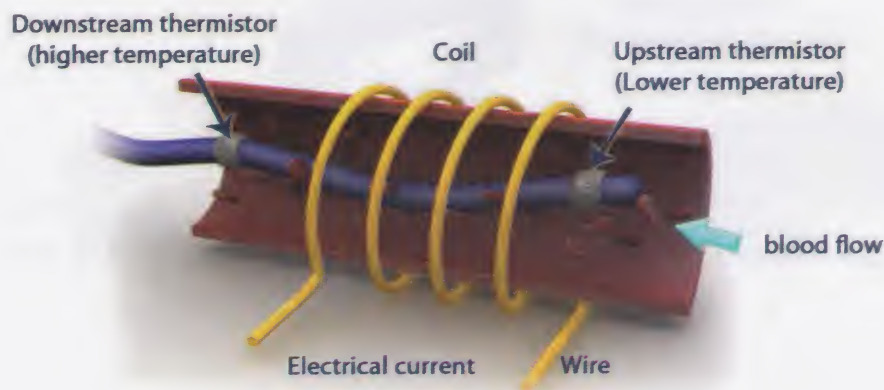


Figure 5-79: Heat dissipation method

b- Measurement of Oscillatory (Pulsatile) Flow:

These methods provide instantaneous measurement of oscillatory (pulsatile) flow. It can also give a measure of average flow per unit time.

1- Methods Based on Pressure Measurement:

Idea: There are two main ideas:

a- Difference in the Pressure between Two Points:

According to the Poiseuille's equation, provided the flow is laminar, the flow can be known if the following parameters are known:

- The difference in the pressure between two points, situated proximally and distally in the vessel, sensed with a double-lumen catheter and a differential electro-manometer.
- The diameter of the blood vessel measured by angiographic techniques.

b- Analysis of the Pulse Wave Contour Recorded by Intraarterial Pressure Measurement:

It is performed by a bedside computer which displays beat-to-beat values for the stroke volume, heart rate and cardiac output.

Disadvantages:

It is inaccurate; therefore, it should be calibrated with one of the standard methods e.g., dye dilution to establish correction factors for each patient.

2- Electromagnetic Flowmeter:

It is the most commonly used direct method.

Idea:

This device depends on the electromagnetic induction phenomenon. As blood or any other electrolyte solution (which is a conductor of electricity) moves at right angles through a magnetic field, an electric potential is induced which is proportional to the velocity of the blood. The potential is induced in a plane perpendicular to both the magnetic field and the direction of blood flow according to Faraday's left-hand rule. By knowing the cross-sectional area of the blood vessel, the flow rate of the blood can be known (figure 5-80).

Disadvantages:

1- It is an invasive technique. The probe is inserted on an intravenous catheter-tip or incorporated into an extracorporeal perfusion circuit.

- 2- For calibration, zero flow is required; therefore, clamping of the blood vessel is needed. This is not possible when the blood flow of the aorta or pulmonary artery is to be recorded; therefore, a recent device is used which produces a pulsed current (in the form of a waveform). With this waveform, there is a period of zero current flow; this can be used to re-zero the instrument automatically.
- 3- The diameter of the blood vessel should be known either radio-graphically or directly before the actual volume flow could be measured.
- 4- The results are affected by the change in the blood pressure and the tone of the blood vessels.

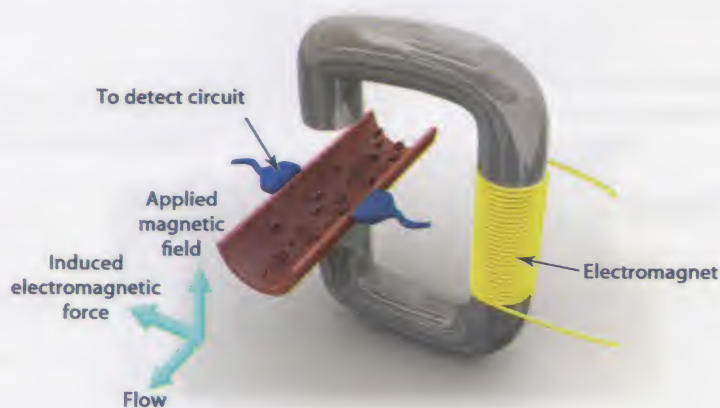


Figure 5-80: Electromagnetic flowmeter

3- Ultrasonic Flowmeter:

Idea:

It utilizes the property of sound transmission through a moving fluid where the characters of the sound waves change with the velocity and the direction of the flow. There are two types:

a- Ultrasound Flowmeter Using Transit Time Difference:

Two transmitter-receiver crystals are placed on opposite sides of the vessel in a diagonal manner. The first transmitter crystal transmits pulses of ultrasound to the downstream receiver while the second transmitter crystal transmits pulses of ultrasound to the upstream receiver. The pulses of ultrasounds are transmitted simultaneously.

There is a difference between the transit time of the pulses transmitted and received by the two crystals. This difference depends on:

- The angle between the transmitter-receiver axis and the direction of blood flow.
- The velocity of the blood flow.

Since the position of the crystals is fixed by the flowmeter; therefore, the angle between the transmitter-receiver axis and the direction of the blood flow is constant and the difference between the transit time is directly related to the blood velocity.

b- Ultrasound Flowmeter Using the Doppler Principle:

A single transmitter-receiver crystal is directed at an angle to the flowing stream. The ultrasound beam is reflected from the moving red blood cells.

If the red blood cells are moving away from the crystal, the ultrasound beam received will have a lower frequency than that transmitted. If the red blood cells are moving towards the crystals, the ultrasound beam received will have a higher frequency than that transmitted. The difference between transmitted and received frequencies is the Doppler frequency which is directly proportional to the velocity of the reflecting surface with respect to the transmitter (figure 5-81).

Advantages: (of Doppler Instruments)

- 1- They can detect the direction and the velocity of the flow.
- 2- They can measure blood flow some distance away from the vessel i.e., at inaccessible sites e.g.,
 - Fetal circulation to monitor fetal heart sound.
 - Placenta to know its extent and site.
 - Deep peripheral veins to detect venous thrombosis in the legs.
 - Pulmonary vessels to detect air embolism.
 - Other deeper tissues.

Disadvantages:

1- These devices can not measure the volume of the flow but only the velocity of the flow i.e., they provide good qualitative but not quantitative information on flow.

N.B: To calculate the volume of the flow, the cross-sectional area of the blood vessel should be known.

2- Ultrasound is reflected by an air-tissue interface so that the transducer must be coupled to the vessel or skin with a liquid or gel acoustic coupling medium.

3- Ultrasound is reflected strongly by bone so that blood flow measurements within the skull are impracticable. Trans-cranial Doppler can be applied over the thin temporal bone except if there is temporal bone hyperostosis.

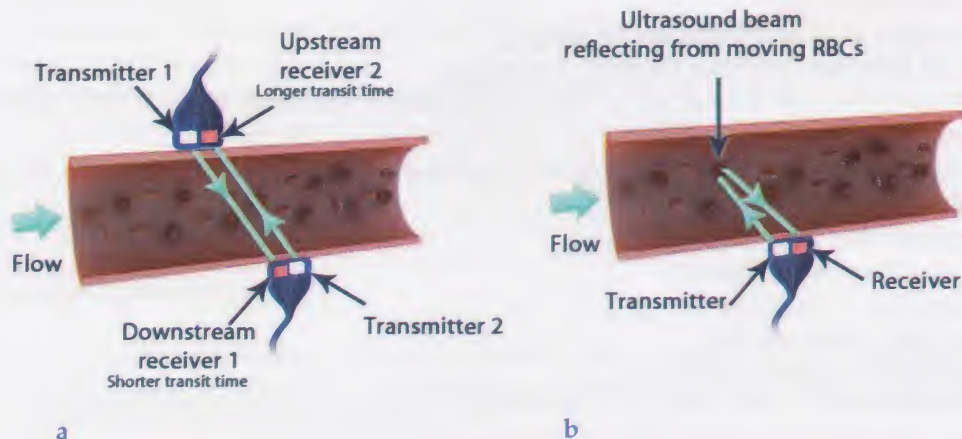


Figure 5-81: Ultrasonic flowmeter; Transit time (a) and Doppler principle

Thin-Film Flowmeter:Idea:

The probe consists of a small glass bead on the end of a catheter. Three thin metallic rings about 1 μm in thickness are deposited on the bead.

The central ring acts as a resistance thermometer and as a heating element. Changes in the flow velocity lead to changes in the temperature of the ring, but the temperature of the ring is kept constant; therefore, the power needed to maintain the temperature of the ring is proportional to the blood flow.

The two end rings are used to detect the direction of flow by sensing the temperature difference produced by the central heated ring (figure 5-82).



Figure 5-82: Thin-film flowmeter

II) Indirect Methods:1- Fick Principle:Idea:

The principle states that the amount of substance or tracer taken up or given off by an organ in unit time is equal to the product of blood flow through the organ and the concentration difference of the substance across the organ.

Amount taken or given/unit time = Flow \times (a - v) content difference

Where a = arterial and v = venous

Therefore, blood flow to any organ = $\frac{\text{Amount taken or given/unit time}}{(\text{a} - \text{v}) \text{ content difference}}$

Clinical Applications:

It is used to measure the blood flow through a variety of organs, including:

- Heart (coronary blood flow)
- Brain (cerebral blood flow)
- Liver (hepatic blood flow)
- Kidney (renal blood flow)
- Lung (total cardiac output or pulmonary blood flow).

2- Dilution Technique:

a) Single Injection Indicator Dilution Technique

b) Continuous Infusion Indicator Dilution Technique

They are discussed later in the chapter of "Monitoring during Anesthesia and Intensive Care".

3- Clearance Methods:

The clearance of any substance is the volume of plasma which supplies the amount of that substance cleared by that organ.

Clinical Applications:

- Cerebral blood flow measurement.
- Muscle blood flow measurement.
- Renal blood flow measurement.
- Hepatic blood flow measurement.

They are discussed later in the chapter of "Monitoring during Anesthesia & Intensive Care".

4- Venous Occlusion (Limb) Plethysmography:

Idea:

This technique includes temporary occlusion of venous outflow from the limb by abruptly pressurizing a proximal cuff to a pressure between the arterial and venous pressure of the limb (about 50- 60 mmHg). This occludes the veins only. The consequent increase in the volume of the limb corresponds to the arterial inflow. The increase in the volume of the limb may be calculated by one of the following methods:

- 1- Volume displacement in a water container or an air tight box in which the limb is sealed and surrounded with air or water at a constant temperature close to that of the skin. The increase in the limb volume is transmitted directly to a small recording spirometer or a pressure gauge.
- 2- The increase in girth of the limb measured by a mercury-in-rubber strain gauge which surrounds the limb. When the rubber tube containing the mercury is stretched, it becomes longer and narrower. The electrical resistance of the column of mercury therefore increases. These changes in resistance can be detected, amplified and recorded.
- 3- The increase in arterial blood flow increases the quantity of ions per unit mass of tissue which, in turn, decreases the electrical impedance and increases the conduction of electricity which can be recorded.

Clinical Applications:

- Measurement of blood flow in a limb, finger, or toe i.e., an appendage.

5- Physiologically Inaccurate Methods:

- Multiple radiographs of the heart.
- Examination of arterial pulse contour.
- Oscillations in the body due to heart beats.

N.B.: Measurement of cardiac output is discussed in the chapter "Monitoring during Anesthesia & Intensive Care".

Liquid and Blood Volume Measurement

1- Measuring Container Method:

It is done simply by collection of the fluid e.g., blood outside the body in a measuring cylinder as in suction units.

2- Dye Dilution Technique:

It is used to measure the plasma volume.

Idea:

A known amount of a dye e.g., Evans blue dye is injected intravenously. After 10 minutes (to allow complete mixing with the plasma), a blood sample is taken and centrifuged.

This dye is non-toxic, non-hemolysing, and non-diffusible to tissues because it is mainly bound to plasma albumin.

The color of the plasma is then matched colorimetrically with different dilutions of the dye.

The volume of plasma can be calculated from the equation:

$$V_1 \times C_1 = V_2 \times C_2$$

Where V_1 = volume of the dye.

C_1 = concentration of the dye before injection of 1 ml of the dye solution.

V_2 = volume of the plasma.

C_2 = concentration of the dye after injection of 1 ml of the dye solution.

By knowing the hematocrit (Hct) value, the volume of the whole blood can be estimated.

$$\text{Blood volume} = \frac{\text{Plasma volume}}{1 - \text{Hct}}$$

5- Radioactive Isotope Dilution Technique:

a- Red Cell Volume Measurement:

Idea:

A known amount or dose of **labelled red cells** is injected into a patient. After they have been mixed thoroughly with the patient's blood, the concentration of the labelled cells may be detected from the radioactivity of a blood sample from the patient:

$$V_1 \times C_1 = V_2 \times C_2$$

Where V_1 = volume of injected labelled red blood cells.

C_1 = concentration of injected labelled red blood cells

V_2 = volume of the patient's red blood cells

C_2 = concentration of labelled red blood cells in the patient's blood.

As $V_1 \times C_1$ = the dose of injected labelled red blood cells

$$\begin{aligned} \text{Therefore, volume of the patient's red blood cells (V2)} &= \frac{V_1 \times C_1}{C_2} \\ &= \frac{\text{Dose of labelled red cells}}{\text{Concentration of labelled red cells}} \end{aligned}$$

b- Plasma Volume Measurement:

Idea:

The same idea as above, but **radioactive albumin** is used instead of labelled red cells.

N.B.: Total Blood Volume Measurement:

It can be estimated by one of the following:

• Total blood volume = red cell volume + plasma volume

• Total blood volume = $\frac{\text{Red cell volume}}{\text{Hematocrit}}$

• Total blood volume = $\frac{\text{Plasma volume}}{1 - \text{Hematocrit}}$

Disadvantages:

• In shocked patients, pooling and stasis of blood may occur in poorly perfused areas; therefore, even mixing of the radioactive indicator may not be obtained.

• In patients with polycythemia, the blood sample hematocrit may be different from the whole body hematocrit; therefore, both red cell volume and plasma volume will need to be measured in order to estimate blood volume accurately.

c- Total Extracellular Volume Measurement:

Idea:

The same idea as above, but **radioactive sodium** is used instead of labelled red cells.

PART 10: PRESSURE

Definitions

Pressure:

- It is the force applied or distributed over a surface.
- It is expressed as force per unit area i.e., Newton per square meter (N/m^2).
- **The S.I. unit of pressure is the pascal (Pa).**

The pascal is a pressure of 1 newton acting over an area of 1 square meter i.e. $1 \text{ Pa} = 1 \text{ N/m}^2$.

As the pascal unit is too small for most physiological applications; therefore, the kilopascal (kPa) is the unit commonly used in clinical practice.

Force:

- It is that which changes or tends to change the state of rest or motion of an object.
- **The S.I. unit of force is the newton (N).**

The newton is the force that will give a mass of 1 kilogram an acceleration of 1 meter per second per second i.e., $1 \text{ N} = \text{kg.m.s}^{-2}$.

• **The force of gravity** acting on any object will give the object an acceleration of 9.81 m.s^{-2} . Therefore, the force of the gravity on a mass of 1 kilogram must be 9.81 N. This force is known as 1 kilogram weight, so 1 newton is equivalent to $\frac{1}{9.81}$ kilogram weight i.e., 102 gram weight.

Other non-S.I. Units of Pressure:

- Atmosphere absolute (ata).
- Pound per square inch (psi).
- Millimeter mercury (mm Hg).
- Torr: It is equal to mm Hg and usually used on vacuum gauges.
- Centimeter water ($\text{cm H}_2\text{O}$).
- Bar: It is a unit used for high-pressure gas supplies.

To change between pressure units:

One atmospheric pressure = 1 atmosphere absolute (ata)
 $= 760 \text{ mmHg}$
 $= 760 \text{ torr}$
 $= 1030 \text{ cmH}_2\text{O}$
 $= 1.01325 \text{ bar (SI unit) i.e., nearly 1 bar}$
 $= 101.325 \text{ kPa i.e., nearly 100 kPa}$
 (kPa is more used more in medical practice as 1 Pa is a very small unit)
 $= 101\,325 \text{ N.m}^{-2}$
 $= 101\,325 \text{ kg.m}^{-1}.\text{s}^{-2}$
 $= 14.7 \text{ pounds per square inch (psi or lb.in}^{-2}\text{)}$

The most commonly used units in anesthetic practice are:

$$1 \text{ kPa} = 0.01 \text{ bar} = 7.6 \text{ mm Hg} = 10.3 \text{ cm H}_2\text{O}.$$

The partial pressures of the atmospheric gases measured in kPa are numerical = the percentage concentration because the atmospheric pressure (100%) = 100 kPa

i.e., 21% oxygen = 21 kPa partial pressure.

79% nitrogen = 79 kPa partial pressure.

The interrelationship of pressure and force

$$\text{Pressure} = \frac{\text{Force}}{\text{Area}}$$

Clinical applications:

1- There is a difference in the pressure during injection through a small syringe and a large syringe. As the force exerted by the thumb is nearly similar during injection by the two syringes, the pressure available for injection is greatly increased in the small syringe because the pressure is inversely proportional to the cross-sectional area of the plunger (figure 5-83).

Thumb pressure on the end of a syringe plunger can produce a force of nearly 25 Newton.

a- In small syringes, the area of the plunger in a 2 ml syringe is 5×10^{-5} square meters, so the pressure generated in the syringes is as follows:

$$\frac{25 \text{ N}}{5 \times 10^{-5} \text{ m}^2} = 500 \text{ kPa}$$

The pressure of 500 kPa is about 5 times atmospheric pressure, so **it is easy to produce extravascular infusion unintentionally with such a small syringe.**

2- In large syringes, the area of the plunger in a 20 ml syringe is 2.5×10^{-4} square meters, so the pressure generated in the syringe can be calculated as above. It is 100 kPa (about 1 atmosphere). This pressure is about 6 times a typical systolic blood pressure of 16 kPa (120 mmHg). Therefore, **during intravenous regional anesthesia**, if a 20 ml syringe is used to inject local anesthesia, especially in a vein near the tourniquet, the local anesthesia may escape from the tourniquet to the systemic circulation as the pressure generated during rapid injection may exceed the pressure in the tourniquet cuff.

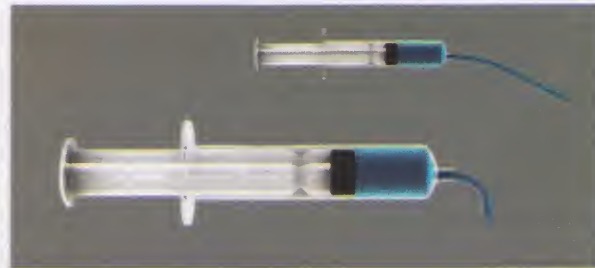


Figure 5-83: Interrelation between the pressure and force

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2- Some syringe pumps and infusion pumps can also generate high pressures; therefore, care should be taken to ensure that cannulas are correctly placed to **avoid extravasation.**

3- **Formation of bed sores:** during prolonged recumbency in bed, bed sores may occur as follows: suppose 20 kg of the patient's weight are supported by an area of contact between the patient and the bed of 10^{-2} square meters (an area equal to 10 cm x 10cm), the force over this area is:

$$= 20 \text{ kg} \times 9.81 \text{ m.s}^{-2} = 196 \text{ N}$$

$$\text{Therefore, the pressure} = \frac{196 \text{ N}}{10^{-2} \text{ m}^2} = 19.6 \text{ kPa}$$

As the typical systolic pressure is only 16 kPa, the blood supply to this area is cut off and ischemia occurs, which leads to occurrence of bed sores.

4- Many devices and valves operate by a mechanism depending on the interrelationship between the pressure and force and surface area e.g.,

- pressure relief valves,
- expiratory valves of anesthetic machines,
- pressure-reducing valves (pressure regulators),
- and • oxygen-failure warning devices.

Atmospheric (Barometric) Pressure (P_B):

• It is the pressure exerted by the atmospheric air due to the gravitational force on air molecules above it, it is the weight of air on unit area of the land.

It is measured by a mercury tube barometer (figure 5-84).

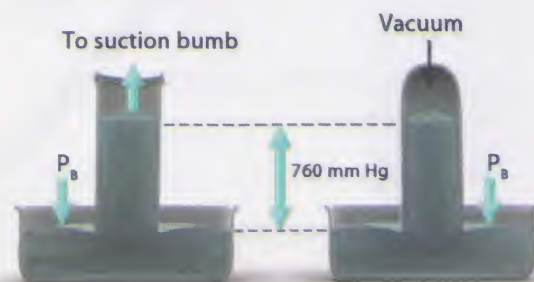


Figure 5-84: Mercury tube barometer

- **Values of P_B :** - At sea level, it is 760 mm Hg.
 - At high altitudes, it is < 760 mm Hg, because the density of the air decreases as we go up, so, the partial pressure of oxygen also falls causing hypoxic hypoxia of high altitudes.
 - In seawater, it is > 760 mm Hg, the P_B increases by one atmosphere for every 10 meters of depth due to the weight of water.

Gauge (Manometric) Pressure:

It is the pressure recorded from the pressure gauge (manometer) where the atmospheric pressure reads zero i.e., the manometer sets the atmospheric pressure as the zero reference point. Any pressure above the zero is called the gauge pressure.

Absolute (True) Pressure:

Absolute pressure = gauge pressure + atmospheric pressure

Clinical Applications:

- In anesthetic practice, the gauge pressure is the one commonly used e.g., ventilator pressure, gas-cylinder pressures, arterial blood pressure, and venous pressure.....etc.
- A full oxygen cylinder has a gauge pressure of 137 bar; therefore, the absolute pressure is 138 bar (137 bar gauge pressure + 1 atmospheric pressure).

An empty oxygen cylinder has a gauge pressure of 0 bar; therefore, the absolute pressure is 1 bar i.e., the empty cylinder still contains oxygen at the ambient atmospheric pressure (1 bar).

- If the pressure inside a hyperbaric chamber is 2 atmospheres, the absolute pressure is 3 atmospheres absolute (3 ata).

- A blood pressure of 120/80 mm Hg (gauge pressure) has an absolute pressure of 880/840 mm Hg (add 760 mm Hg to each value).

- The sub-atmospheric pressure is less than 760 mm Hg e.g., 750 mm Hg. It is indicated by a minus sign i.e., - 10 mm Hg. This means 10 mm Hg below the atmospheric pressure.

Differential Pressure:

Is the difference in pressure between two pressures e.g., between two points in an anesthetic breathing system.

Measurement of Pressure

Includes:

- 1- Liquid manometers: - Mercury manometer.
- Saline manometer
- 2- Mechanical pressure gauges: 1- Bourdon gauge.
2- Aneroid gauge.
3- Diaphragm gauge.

Liquid Manometers:

Idea:

The force exerted by a column of fluid = mass x gravity

As Mass = volume x density,

Force exerted by a column of fluid = volume x density x gravity

As volume = height x cross-sectional area of liquid,

Force exerted by a column of fluid = height x cross-sectional area of liquid x density x gravity

As pressure = force/cross sectional area,

$$\text{Pressure} = \frac{\text{height} \times \text{cross-sectional area} \times \text{density} \times \text{gravity}}{\text{cross-sectional area}}$$

So, pressure = height x density x gravity

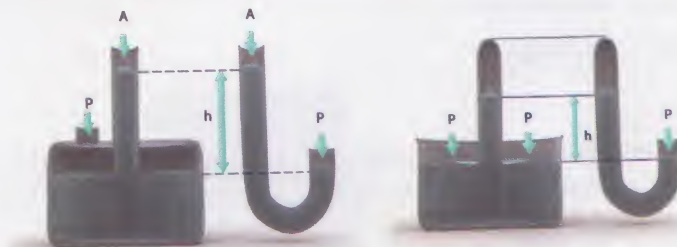
Manometers have either:

a- An open-ended tube:

The tube has an end open to the atmosphere. It is used to measure **the gauge pressure**; therefore, it is used to measure the blood pressure. A disc of a material permeable to air is placed at the top of the tube to prevent spillage of the mercury, but this creates a potential problem in that dirt or grease may partially obstruct the disc, thus leading to faulty readings (figure 5-85).

b- A sealed-ended tube (barometer):

The tube has a sealed end and is not connected to the atmosphere. It is used to measure **the absolute pressure** i.e., atmospheric pressure and gauge pressure where a vacuum is present above the mercury.



P = applied pressure, h = measured pressure, A = atmospheric pressure

Figure 5-85: Manometer tubes; open-ended (left) and sealed-ended (right)

Factors Affecting the Readings of Liquid Manometers:

1- Surface Tension:

It increases the reading in water manometers because the forces between the water molecules and the walls of the container cause a concave meniscus.

It decreases the reading in the mercury manometers because the forces between the molecules and the walls of the container cause a convex meniscus.

2- Effect of the Slope of the Tube:

If the tube of the manometer is inclined, small changes in the pressure (P) produce a small difference in height between the two menisci (h), but this is amplified on the scale (L) (figure 5-86).

N.B.: The pressure is not affected by the diameter of the manometer tube.

Examples:

1- Mercury Manometer:

Mercury is 13.6 times as dense as water, so the force exerted by its weight is proportionately greater. A pressure which supports a 7.6 mm column of mercury will support a 10.3 cm column of water.

The pressures in the two manometers may be compared as follows:

$$\begin{aligned} \text{Pressure exerted by 7.6 mmHg} &= 13.6 \times 7.6 \text{ mmHg} \\ &= 10.3 \text{ cmH}_2\text{O} \\ &= 1 \text{ kPa} \end{aligned}$$

Clinical Applications:

It is ideal for arterial blood pressure measurement (figure 5-87).

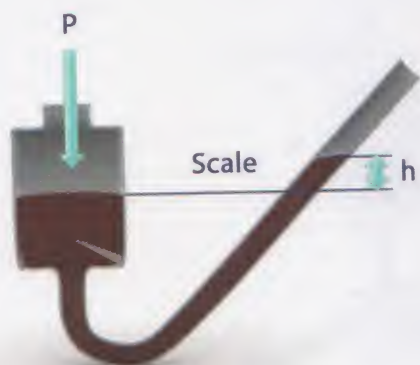


Figure 5-86: Inclined plane manometer; a small pressure (P) produces a small difference in height between the two menisci (h), but this is amplified on the scale



Figure 5-87: A mercury manometer

2- Saline Manometer:

Idea: the same idea as above.

Clinical Applications:

It is ideal for venous pressure measurement.

Mechanical Pressure Gauges:**1- Bourdon Gauge:**

Idea:

It consists of a coiled tube which is flattened in cross-section. One end of the coil is anchored to the case and connected to the source of pressure, while the other end is closed and attached to a mechanism which drives the pointer across the dial (figure 5-88).



Figure 5-88: Bourdon gauge

The application of pressure to the inside of the tube causes the cross-section to become more circular. This causes the coil to straighten. Since one end is fixed, the other unwinds and so moves the pointer across the dial.

Clinical applications:

It is mainly used for measurement of high pressures. It is also adapted for the measurement of temperature and flow (see before).

2- Aneroid Gauge:

Idea:

A metal bellows is used to sense smaller pressure where expansion of this bellows is detected by a lever mechanism which amplifies the movement and drives the pointer across the scale (figure 5-89).

N.B.: "a-neros" is a Greek word meaning without liquid.

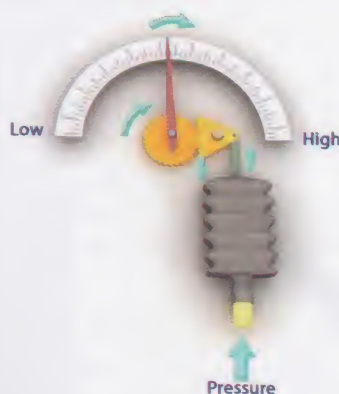


Figure 5-89: Aneroid gauge

Clinical Applications:

- It is used to measure • blood pressure.
• pressure of mechanical ventilators.

3- Diaphragm Gauge:

Idea:

The pressure causes movement of a flexible diaphragm. This movement is sensed by many methods:

1- Direct method:

The movement is detected by attaching a thread or lever to the center of the diaphragm, and the other end is connected to a pointer or writing arm. It is not very sensitive.

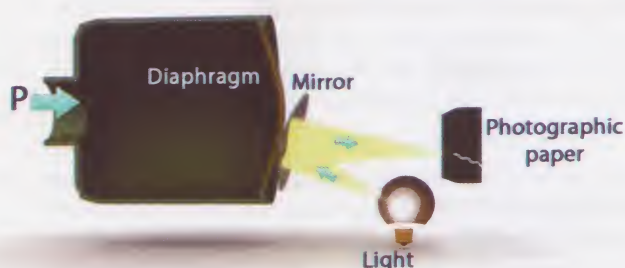
2- Optical method: (figure 5-90)

Figure 5-90: An optical method to detect the movement of the diaphragm

A small mirror is attached to one side of the diaphragm. When the diaphragm is stretched by the application of pressure, it becomes curved and the mirror is rotated. The displacement of the mirror is recorded as it reflects a beam of light onto a moving photographic paper. It is very sensitive.

3- Electromechanical method (pressure transducer):

A transducer is the device which converts energy from one form to another.

Therefore, a **pressure transducer** converts pressure energy into electrical energy. It is often called **electromanometer**.

Clinical Applications:

It is used for the most physiological pressure measurements.

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Pressure Transducers:**1- Optical Transducer (Optical Defocusing Manometer):**Idea:

A diaphragm with two silvered surfaces is exposed to a light source where the beam of light will be reflected from both silvered sides of the diaphragm to fall onto two photoelectric cells in front of each surface. When the diaphragm is exposed to a pressure, the silvered surfaces are moved where one surface becomes convex while the other is concave. The convex surface causes the reflected light beam to diverge, so that the intensity of light sensed by the photoelectric cell decreases and its electrical output falls, while the other concave surface causes the beam of light to converge, so that the intensity of light sensed by the other photoelectric cell increases and its electrical output rises. Presence of two silvered sides instead of one side greatly increases the sensitivity (figure 5-91).

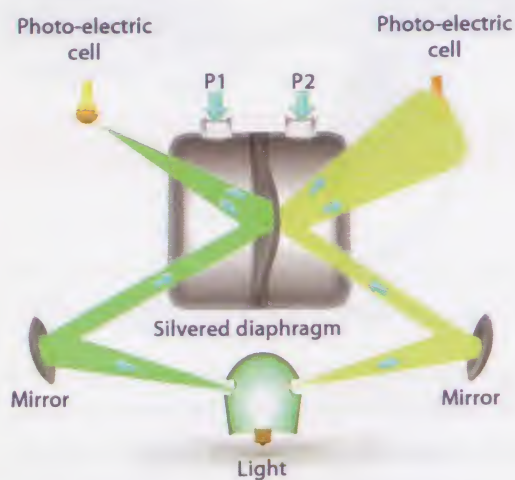


Figure 5-91: Optical transducer

Clinical Applications:

It is used for intravascular pressure measurement where the diaphragm is situated at the end of the fiberoptic bundle that lies within a cardiac catheter. Light is transmitted to the diaphragm by one section of the fiberoptic bundle.

2- Wire Strain Transducer or Gauge (Variable Resistance):Idea:

When a wire is stretched or compressed, its electrical resistance changes. This change in the resistance is produced by changes in the length and diameter of the wire and by changes in the atomic structure of the metal.

There are two types:

a- Unbonded Wire Strain Gauge: (figure 5-92)

The resistance wires are stretched between a fixed point and a movable block attached to the diaphragm. The resistance wires are arranged in two sets, so that the application of pressure stretches one set and compresses the other. The difference in the resistance between the two sets is measured by a Wheatstone bridge system, so that the output voltage is proportional to the displacement of the diaphragm.

b- Bonded Wire Strain Gauge: (figure 5-93)

The resistance wires are arranged in a zig-zag pattern and cemented to the back of the diaphragm. The wire is either cemented to one side of the diaphragm or to both sides of the diaphragm, so increasing the curvature of the diaphragm stretches one gauge and compresses the other.

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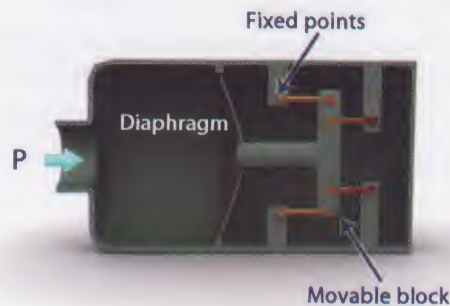


Figure 5-92: Unbonded wire strain gauge

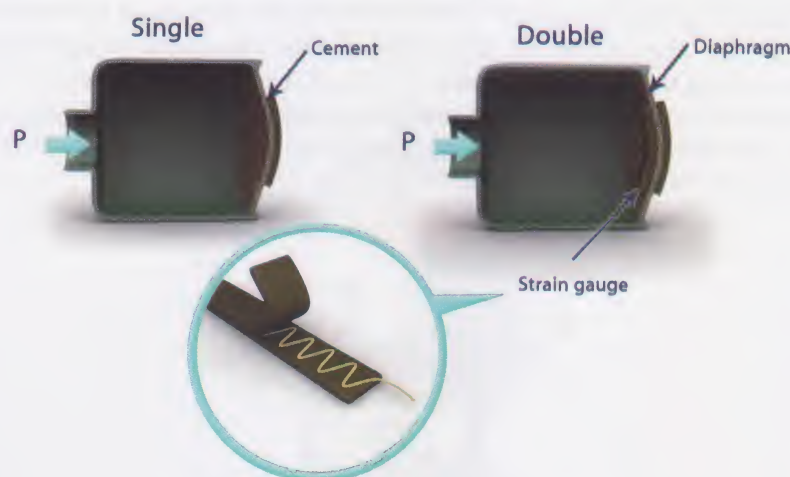


Figure 5-93: Bonded wire strain gauge

3- Silicon Strain Transducer or Gauge:Idea:

It is nearly the same as the wire strain gauge, but has higher sensitivity. An extremely thin slice of a silicon crystal is bonded onto the back of the diaphragm where the silicon crystal changes resistance as it

is compressed or expanded when the diaphragm changes in shape. The resistance is sensed with a Wheatstone bridge circuit.

4- Capacitance Transducer:

Idea:

The diaphragm of the pressure transducer is used as one plate of a capacitor, while the second plate is fixed. Movement of the diaphragm varies the distance between the plates, and this varies the charge which can be carried by the capacitor. This is sensed by a Wheatstone bridge circuit energized by an alternating current.

5- Inductance (Electromagnetic) Transducer:

Idea:

The inductance of a coil can be varied by changing the position of a core of magnetic material lying within the magnetic field of the coil. The magnetic core is attached to the diaphragm and the inductance of the coil is measured by making it part of a Wheatstone bridge circuit which is energized by an alternating current (figure 5-94).



Figure 5-94: Inductance transducer

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Differential Pressure Transducers:

Idea:

When two different pressures are applied on both sides of the diaphragm and measurement of the difference between the two pressures is recorded, this is known as a differential transducer.

N.B.: Most pressure transducers are designed to measure a pressure applied to one side of a diaphragm, while the other side of the diaphragm is at atmospheric pressure. This is known as single-ended transducers.

Clinical Applications:

- Measurement of the difference between airway and esophageal pressures.
- Measurement of the difference between the two sides of a pneumotachograph screen.
- Measurement of the difference between intravascular and esophageal pressure (i.e., measurement of transmural pressure differences within the thorax).

Measurement of Blood Pressure

It is discussed in details in the chapter of "Monitoring during Anesthesia & Intensive Care".

PART 11: ELECTRICITY

Definitions

Electricity:

Is a form of energy produced by induction or by chemical means, and can produce magnetic, thermal, and chemical effects. An electric current is a flow of electrons through a conductor in a closed electric circuit.

Static Electricity:

Is the phenomenon which occurs on rubbing amber (or other non-conducting substances e.g. plastics and rubber) against another non-conducting material leading to transfer of electrons, so that one of the substances will have excess electrons and the other a deficit. This phenomenon may also occur in chemical reactions in batteries, and in biological tissues.

Static electricity can be a source of ignition in anesthetic explosions.

Potential Energy:

The electrons in the objects with excess electrons have potential energy in the same manner that the height of an object determines its gravitational potential energy.

The difference in electrons between objects with excess electrons (relatively with more negative charges) and that with the deficit (relatively with more positively charges) makes an **electric potential difference**.

N.B.: - The word electricity is derived from "elektron", the Greek word for amber.

- The atoms of all substances including amber consist of a central nucleus containing positively charged protons and neutral neutrons surrounded by negatively charged electrons which spin in orbits around the nucleus.

Electronics:

It is a technology based on the behavior, properties, and control of electrons. Electronic techniques are used in many fields including medicine, communications, computers, defense, industry, and entertainment (radio and television).

Direct and Alternating Current

Direct Current (DC):

It is a current where electrons flow in one direction.

It is produced by thermocouples or batteries. In a battery, chemical energy is converted into electrical energy through a chemical reaction.

Alternating Current (AC):

It is a current where electrons periodically reverse their direction, first in one direction and then in the opposite direction.

AC can be represented by a sine wave, which has three characteristic features (figure 5-95):

- **Wavelength:** is the distance between the beginning and the end of the sine wave, or, it is the distance between two successive positive or negative peaks. It covers a complete cycle of 360°.

- **Frequency:** is the number of waves per second. Cycle/second = hertz (Hz).

The mains domestic electricity is 50 Hz in UK and 60 Hz in Egypt and USA.

- **Velocity:** wavelength x frequency.

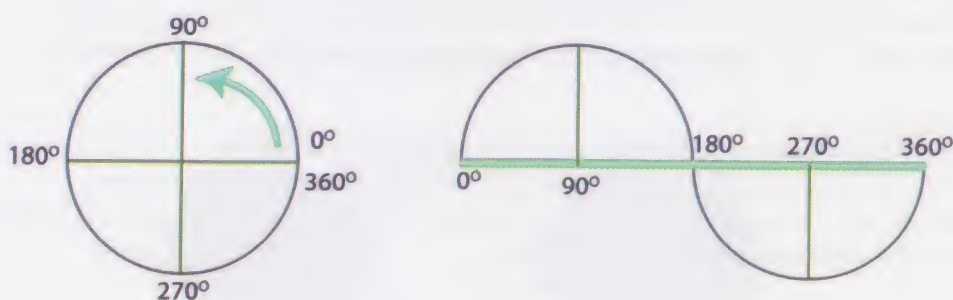


Figure 5-95: Alternating current

Ohm's Law:

It states that the current flowing through a conductor is proportional to the electromotive force causing that current.

$$I = \frac{E}{R}$$

or

$$R = \frac{E}{I}$$

or

$$E = I \times R$$

Where I = the current measured in amperes.

E = the potential difference or the electromagnetic force (voltage) measured in volts.

R = the resistance measured in ohms.

The triangle in figure 5-96 is a memory aid to remember Ohm's law. Cover the unknown value with a finger tip, and the triangle will reveal the correct formula.

For example, if you want to know the current, cover the letter I and the formula is revealed as E divided by R.

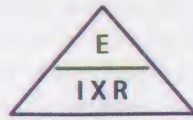


Figure 5-96: Ohm's law

Current Flow and Energy Production:

• When a current flows, heat and sometimes light energy are produced. In order to drive the electric current through the light bulb, a potential difference must be present across the bulb. The unit of potential difference is the volt, and this is based on energy production and current flow.

$$\text{Potential difference in volts (V)} = \frac{\text{Power in watts (W)}}{\text{Current in amperes (A)}}$$

Therefore, **the volt** is defined as the potential difference which produces a current of one ampere in a substance when the rate of energy dissipation is one watt.

• The rate at which the energy (heat or light) is produced depends on the current and the potential difference.

• The heat production produced by an alternating current (AC) with a maximum of 1 ampere is smaller than that produced by a constant current (DC) of 1 ampere because in the case of AC, the peak flow occurs for only a small fraction of the time; while in the DC, the peak flow is constantly at a high level.

Clinical Applications:

1- In an emergency DC-powered operating theater light, the energy production of heat and light could be 96 watts or 96 joules of energy per second.

$$\text{Potential difference} = \frac{96 \text{ W}}{4 \text{ A}} = 24 \text{ V}$$

2- In fuses that are used to protect electrical equipment against a sudden increase in the electric current.

A fuse is a wire of a diameter chosen so that if the current exceeds the rating of the fuse, the wire rapidly heats (i.e., sudden increase in electric current causes increase in heat production) and then melts; stopping the flow of current and so the electrical equipment is protected.

For the safety of an electrical apparatus, it is essential that the correct size of a fuse (i.e., the correct size of the wire) is used.

Conductors, Insulators, and Semiconductors

Under the effect of a potential difference (or a changing magnetic field) electrons can pass from one atom to another and an electric current is the movement of such electrons through a substance.

Substances are classified into conductors, insulators and semiconductors according to their ability to conduct electrons (electric current):

Conductors: allow the free passage of electric current through them where the outer electrons of their atoms are loosely bound and can readily move through the conductor under the effect of an electric potential, for example, - Metals as copper, lead, tin, platinum, gold, and silver.

- Carbon.

- Liquids as saline and body fluids: as they contain positively and negatively charged ions, which can move easily under the effect of an electric potential.

Insulators: do not allow the passage of an electric current, as their electrons are firmly bound and so are not normally able to move and form an electric current, for example, glass, plastic, rubber, wood, mica, porcelain, and ceramic.

Semiconductors: allow conductivity intermediate between that of conductors and insulators, as the outer electrons are bound to atoms less firmly than in insulators and less loosely than in conductors. Therefore, if a little extra energy is given to these electrons, they escape from the atom they are bound to and hence conduct electricity, for example, silicon, germanium, and selenium.

Clinical Applications of Semiconductors:

Thermistors, transistors, diodes, and photo-detectors are semiconductors.

1- In a **thermistor** (a device used in temperature measurement), heat is the source of extra energy given to the electrons. As the temperature increases, more electrons escape and so the conductivity increases i.e.

the resistance of the thermistor (e.g., made of silicon) is decreased with rise of temperature. This is termed "with negative thermal coefficient of resistivity".

N.B.: Other conductors (e.g., platinum) have a resistance which increases with rise of temperature. They are called "with positive thermal coefficient of resistivity".

2- **Anesthetic monitoring equipment containing semiconductors** are adversely affected by excessive heat in operation rooms.

3- A **photo-detector** is a special type of semiconductor in the form of a resistor, diode or transistor.

When radiation falls on the detector, electrons in the material absorb some of the energy of radiation (i.e., extra energy) and are able to move via the material core freely causing a change in the electric current.

Magnetic Field

Definitions:

- **Magnetism:** is the property of a conductor, as when a current flows through the conductor a force is exerted on another conductor carrying a current.

N.B.: Some substances e.g., iron alloys, can exhibit magnetism although it appears that no current is flowing through them (a magnet). This is due to the sum of the many minute currents formed by the motion of electrons around their nuclei.

- **Magnetic field:** is the region through which a current-carrying conductor or a magnet exerts its magnetic effect.

- **Magnetic field strength:** is the power of the field in vacuum.

- **Magnetic flux:** is the field which results when a magnetic field is present in any material.

The magnetic flux is **greatly increased** over the original magnetic field strength in **ferromagnetic materials**.

The magnetic flux is **slightly increased** over the original magnetic field strength in **paramagnetic materials**.

The magnetic flux is **decreased under** the original magnetic field strength in **diamagnetic materials**.

The unit of magnetic flux is the **weber (Wb)**.

The unit of magnetic flux density is the **tesla (T)** $\text{tesla} = \text{Wb/m}^2$

Clinical Applications:

The magnetic flux density produced by magnetic resonance imaging (MRI) equipment is in the range of 0.2-4 T which is much greater than that produced in the air by the earth's magnetic field which is about 60 μT .

Electromagnetic Force

There are interactions between an electric current and a magnetic field:

- If an **electric current** flows in a wire (a coil), an associated **magnetic field exists** around the wire. This magnetic field produced can be increased if a piece of a suitable magnetic material such as iron is placed into the core of the coil. These substances are called **ferromagnetic materials e.g., iron**.

- If the **magnetic field is changed**, the electrons in a conductor flow **causing an electric current**.

- If a wire carrying **an electric current is placed in a magnetic field**, there is a **force** which tends to move it in a direction perpendicular to both the electric current and the magnetic field. This force is called the **electromagnetic force**.

Clinical Applications:

1- **A galvanometer:**

It is used for recording data in many medical equipment.

A coil of wire is suspended in a magnetic field. The current to be measured passes through this coil and the interaction between the electric current and the magnetic field causes the coil to rotate. The rotation of the coil is proportional to the electric current passing through it and is indicated by a pointer which moves over a scale (figure 5-97).

2- **An electromagnetic blood flowmeter:**

It is used for recording the blood flow.

If a conductor (e.g., blood in an artery) is moved through a magnetic field (produced by the current-carrying coils A and B where the field is perpendicular to the flow of blood), an electric potential develops.

This electric potential is perpendicular to both the direction of flow and the magnetic field i.e., it is developed across opposite walls of the artery. It is measured by two electrodes, C and D, touching

opposite sides of the artery. The magnitude of this induced potential is proportional to the rate at which the conductor is moved through the magnetic field (figure 5-98).

Electronic Circuits

Definition of Electronic Circuits:

It is a closed path around which electrons flow. An electron flow (or current) occurs only when a closed path exists. The electronic circuit is the basic structural unit of electronics.

Components of Electronic Circuits:

An electronic circuit may consist of the following components:

- 1- Source of energy.
- 2- Resistor which has the property of resistance.
- 3- Capacitor which has the property of capacitance.
- 4- Inductor which has the property of inductance.
- 5- Semiconductor.

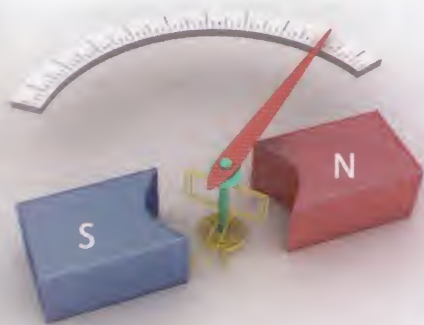


Figure 5-97: A galvanometer

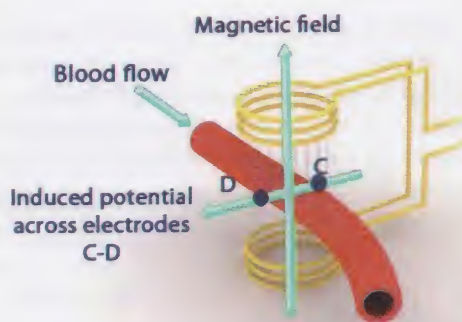


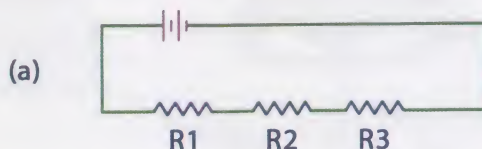
Figure 5-98: An electromagnetic blood flowmeter

1- Source of Energy:

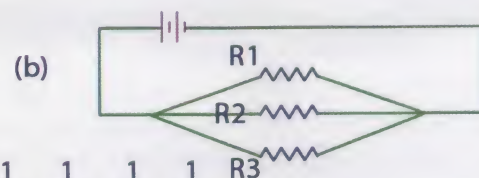
This may be - a direct current (DC) from a battery,
or - an alternating current (AC) from the main power source.

2- Resistor:

- It resists the flow of current through it, and dissipates power by converting electric energy into heat. This property is called resistance. The conversion is irreversible.
- Resistors may be arranged in series or in parallel (figure 5-99).
- The ohm (Ω) is the unit of the resistance.
- Ohm's law is discussed above.
- To monitor or measure the changes of resistance, Wheatstone bridge is used, see later.



$$R = R_1 + R_2 + R_3$$



$$\frac{1}{R} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3}$$

Figure 5-99: Resistors in series (a) and in parallel (b)

Clinical Applications:

Electrical resistance is analogous to flow resistance; potential taking the place of pressure and current taking the place of flow. Like flow resistance, electrical resistance is affected by:

- **Temperature:** a rise of the temperature increases the resistance of a wire resistor but reduces that of many semiconductors. This fact is used in **temperature measurement** and in **thermal conductivity detectors**.
- **Stretch:** a stretched wire becomes longer and thinner and therefore; its resistance increases. This fact is used in **strain gauges** and in **pressure transducers**.

3- Capacitor (Condenser):

• It is a device which stores electric charges, known as the **dielectric**. It consists of two parallel metal plates (two conductors) separated by an insulator. A capacitor cannot conduct electrons directly across the gap between the plates. Therefore, when a **direct current** is applied to an uncharged capacitor, some current will flow at first to charge up the capacitor plates, but will die away as the capacitor becomes fully charged; and a potential difference, and an electric field will be present between the two plates. When the capacitor discharges, the energy returns to the circuit in the form of electron flow (back potential).

• **Capacitance** is the capacity of an object (a capacitor) to hold electric charge. Charge is a measure of the amount of electricity.

• **The coulomb (C)** is the SI unit of charge; it is the quantity of electric charge which passes some point when a current of one ampere flows for a period of one second.

Coulombs (C) = Amperes (A) x Seconds (s)

One coulomb is an amount of electricity equivalent to 6.24×10^{18} electrons.

• **The farad (F)** is the unit of capacitance; it is the capacitance of an object for which the electrical potential increases by one volt when one coulomb of charge is added to it.

Farads (F) = $\frac{\text{Coulombs (C)}}{\text{Volts (V)}}$

i.e., one coulomb of electricity (which passes when 1 ampere flows for 1 second) will charge a 1 farad capacitor to a potential of 1 volt.

- The property of capacitance depends on:

• **The area of the plates:**

A large capacitor holds more electrons than a smaller one and takes longer time to charge or discharge.

• **The resistor in the circuit:**

The higher the resistance, the slower the rate of charge or discharge of the capacitor.

- Clinical applications of capacitance:

- The defibrillator (see later).
- The pressure transducers (capacitance type).
- Interference of the alternating current of the theater light with the ECG trace (figure 5-100):

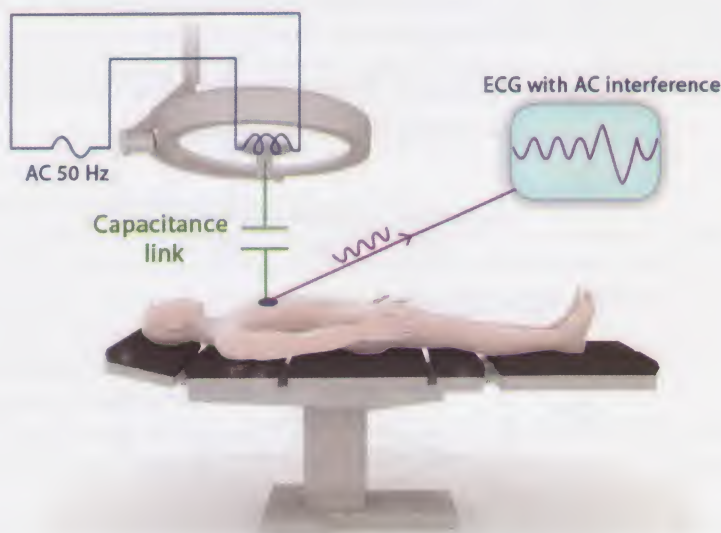


Figure 5-100: Interference on an ECG trace resulting from capacitance

When an alternating current is applied to the capacitor, the alternating current will pass (unlike the direct current), as it is continuously being charged and discharged, hence allowing current to flow across an air gap due to the capacitance. Therefore, in operating rooms, although an operating room light, with main electricity of 50 Hz, is separated from the patient on the operation table by an air gap, a small mains frequency current passes from the lamp (which acts as one capacitor plate) to the patient (which acts as the other capacitor plate) producing a 50 Hz voltage which appears on the ECG trace. This interference may be of sufficient amplitude to obscure the ECG recording.

4- Inductor:

- It is the magnetic analogue of the capacitor because it stores energy in the magnetic field generated by current flowing through it.

When a current flows through a wire coil, it induces a magnetic field around it, which is proportional to the current. Inductance introduces a kind of inertia into the circuit.

- An inductor acts like a brake, since it slows down any change of current, irrespective of whether the current is increasing or decreasing.

In the capacitor, the charge potential is maximal and the current is zero, when a steady electromagnetic force is applied; while in the inductor, the current is maximal and the charge potential across it is zero under the same conditions.

- The unit of inductance is the **henry (H)**.

Clinical Applications:

- The transformer which is found in many of the main-operated apparatus is an example of inductors. Transformers step down the main voltage to low voltage for transistor circuits.

If two coils A and B are placed close together and a current is passed through a coil A, the changing magnetic field will induce an electromagnetic force in coil B. This is called mutual inductance (figure 5-101). The voltage of the alternating electromagnetic force in coil B is related to that in coil A by the ratio of the number of turns in each coil. Thus, if A = 100 turns and B = 10 turns, the voltage across B will be 10 times smaller than that across A.

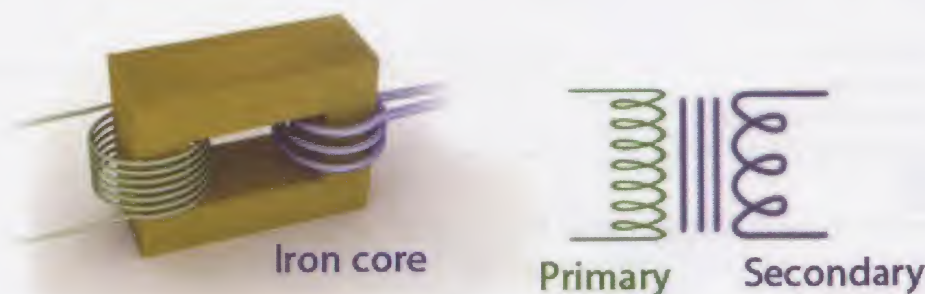


Figure 5-101: Mutual inductance (the transformer)

- **Inductive coupling:** The magnetic field formed by the transformer in a nearby electrical apparatus induces an electric current in the ECG leads or in other biological signal displays, which may lead to interference appearing on the tracing. This interference is called inductive coupling.

Interference from inductive coupling and capacitance effects can be reduced by a system known as screening. The insulated patient monitoring leads are covered by a sheath of woven metal which is earthed, so that interference currents are induced in this metal screen and not in the signal leads. The screening layer is covered by a further layer of insulation.

- **Pressure transducers (inductance type).**

N.B: Signal-to-Noise Ratio:

The electrical interference from the capacitance and inductance effects are called "noise" from analogy with acoustics, in which noise may be regarded as an unwanted sound of various frequencies.

When the signal-to-noise ratio is high, the interference is decreased and the reverse is true with low signal-to-noise ratio. To increase the signal-to-noise ratio:

- reduce the noise to minimum by eliminating its source,
- or - use an electronic filter to cut out the high-frequency electrical interference.

5- Semiconductor Components:

They include:

- **Transistors:** A transistor is a small semiconductor device which amplifies small electric currents. It is a power amplifier and its degree of amplification may reach 100 times. It has replaced the vacuum tube (therm-ionic valve) as an amplifier in electronic circuits. The transistor has the following advantages over the vacuum tube:
 - It does not require a hot cathode or vacuum insulation.
 - It has a small size and a high degree of amplification.
 - It needs much less electric power, and no warm-up time.
 - It produces no heat.
- **Thermistors:** A thermistor is a very small semiconductor device. It is a thermal resistor or temperature-sensitive resistor. It is included in the electronic circuit to correct the current behavior when the temperature fluctuates.
- **Transducers:** A photo-electric cell or transducer is commonly used in the electronic circuit to convert light energy into electric energy. Photo-electric cells use selenium as the semiconductor material because when selenium is exposed to light, it liberates photoelectrons which produce an electric current.
- **Diodes:** A semiconductor diode is a unidirectional device which passes current in one direction, but not in the other. It is used to rectify an AC to DC, thus allowing unidirectional current flow in the electronic circuit i.e., it is used as a rectifier which allows signals of one polarity to flow, but rejects signals of the opposite polarity.

Impedance (Z)

It is **the total opposition** offered by the components of the circuit. There are 3 sources of opposition to the flow of AC in the circuit:

- 1- **Resistance** offered by the resistor which is not affected by the frequency of the current.
- 2- **Inductive reactance** offered by the inductor through which a low-frequency current passes more easily than a high frequency one.
- 3- **Capacitance reactance** offered by the capacitor through which a high-frequency current passes more easily than a low-frequency one.

$$Z = \sqrt{R^2 + (X_L - X_C)^2}$$

Where Z = impedance.

R = resistance.

X_L = inductive reactance.

X_C = capacitance reactance.

Reactance

It is the opposition to the flow of AC caused by a **capacitor or inductor** in the circuit.

N.B.: The unit of impedance is the same as that of the resistance i.e., **the ohm**.

Clinical Applications:

- **Some types of electrocauteries** contain an **isolating capacitor** which offers **high impedance** to the mains frequency current and so, protects the patient from electrocution.
- **During recording a biological electrical signal such as the ECG** through the patient's skin to the electrode, high skin impedance is present that may attenuate the signal.

Therefore, impedance becomes low by the **typical ECG electrode** which:

- consists of a metal disc covered with conductive electrode gel,
- is fixed to the patient's skin by a surrounding adhesive flange.

High impedance and then attenuation of signals occur when:

- the electrode gel is dried,

or - the electrode is loosely attached to the patient's skin.

- **The galvanic skin response:** This test uses skin impedance in measuring the autonomic activity of the patients where skin impedance is lowered when the skin is moist. The degree of moisture depends on the sympathetic tone.

Electrostatic Charge

An electrostatic charge can build up on the surface of any object insulated from its surroundings i.e., unearthed.

When a charged body is brought close to an uncharged one, an equal and opposite charge develops on the uncharged body if it is unearthed.

The ability to store charge is present in the capacitor and the electrostatic charges.

Clinical Applications:

- **In the bobbin of a variable orifice flowmeter**, friction may result in electrons being removed from the bobbin surface when it rotates against the wall of the flowmeter. The resulting opposite electric charges on the wall and bobbin can exert a force of attraction leading the bobbin to stick. This can lead to false high reading of the flowmeter.
- **In the insulators**, electrostatic charges may develop on the surface of the insulators, with risks of sparks, which can be dangerous in the presence of flammable inhalational agents.
- **In an unearthed patient**, when any object such as a cable or operation room lamp element is connected to the mains supply with a fluctuating potential between ± 339 V at a frequency of 50 Hz, the patient will develop a surface charge of equal and opposite potential even though no current is actually flowing between them. The patient acts as one plate of a capacitor (see above).

Wheatstone Bridge

Contents:

It is an electric circuit containing:

- A set of 4 resistors; R_1 , R_2 , R_3 (adjustable), and R_X (unknown).
- A source of electric potential e.g., a battery that is connected across one diagonal of the circuit.
- A galvanometer that is connected across the other diagonal of the circuit (figure 5-102).

The electric current passes through both limbs of the bridge. Some current will also flow through the galvanometer.

To know the value of the unknown resistor (R_X), the adjustable resistor (R_3) which is a variable resistance is adjusted until the galvanometer reads zero. In this condition, the Wheatstone bridge is said to be **balanced** and the voltage across the galvanometer is zero i.e., no current flows through the galvanometer and the system is called null deflection system.

When the circuit is balanced, the following occurs:

$$\frac{R_1}{R_2} = \frac{R_3}{R_X} \quad \text{or} \quad R_1 \times R_X = R_2 \times R_3$$

Thus the unknown R_X can be calculated $R_X = \frac{R_2 \times R_3}{R_1}$

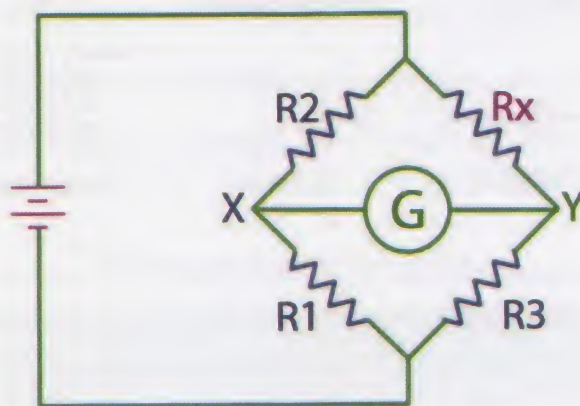


Figure 5-102: Wheatstone bridge

Clinical Applications:

The Wheatstone bridge circuit is applied in the following devices:

- 1- Variable resistance pressure transducers.
- 2- Silicon strain gauge pressure transducers.
- 3- Platinum resistance thermometers.
- 4- Thermistor thermometers.
- 6- Katharometers which are thermal resistors used as detectors for gas chromatography to measure inorganic gases.

Electronic Units

Physical Quantity	Unit		Remarks
	Name	Symbol	
A) Basic unit of Sytème Internationale d'Unités (SIU): • Electric current (It is one of the seven basic SIU)	Ampère	A	
B) The Derived Units: they are derived from SIU • Frequency	Hertz	Hz	1 Hz = 1 cycle/s
• Power	Watt	W	1 W = J.s ⁻¹
• Electric charge, quantity of electricity	Coulomb	C	1 C = s.A.
• Electric tension • Electric potential (voltage)	Volt	V	1 V = W.A ⁻¹
• Electric resistance, reactance, impedance	Ohm	Ω	1 Ω = V.A ⁻¹
• Electric conductance	Siemens	S	1 S = A.V ⁻¹
• Electric inductance	Henry	H	
• Electric capacitance	Farad	F	1 F = C.V ⁻¹

Electrical Symbols

They are shown in figure 5-103.

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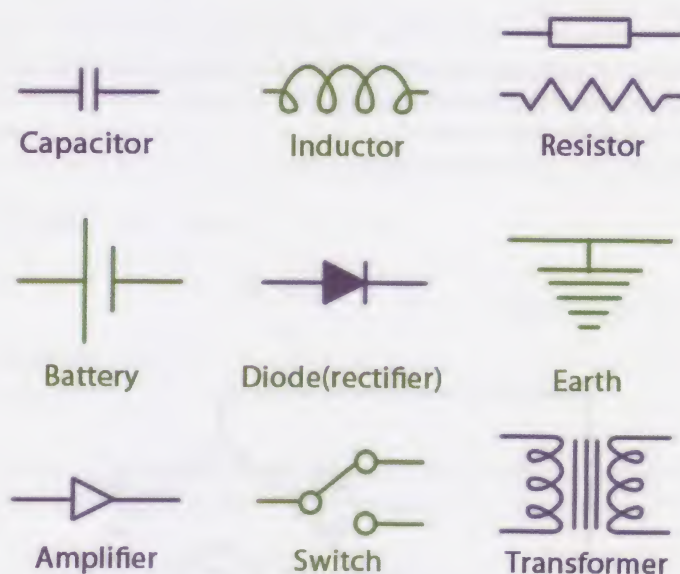


Figure 5-103: Electrical symbols

Electric and Electronic Equipment

Surgical Diathermy (Electrocautery or Electrosurgery)

Idea:

- The passage of direct current or low frequency alternating current through the body may:
 - cause physical sensation,
 - stimulate muscular contraction,
 and - give a risk of ventricular fibrillation.
- These effects become less as the frequency of the current increases:
 - When the frequency is above 1 kHz, these effects are small.
 - When the frequency is above 1 MHz, these effects are negligible.
- The heating and burning effects can occur at all frequencies. The degree of heating and burning produced depends on the **current density**. Current density is the current flow per unit area.

• Therefore, the surgical diathermy operates by generating very high frequency currents in a range of 0.1-3 MHz (megahertz) compared with home line power (50-60 Hz) through the body in order to allow cutting and coagulation by local heating of the body tissues.

Types:

1. Unipolar (Monopolar) Diathermy:

It consists of two electrodes:

• **One active electrode:**

It is the cautery tip used by the surgeon. It has a very small surface area at its tip to produce high current density for cutting or coagulation.

• **The return electrode:**

It is the **patient's plate** that is formed from a large dispersive metal plate which may be covered by a pad well soaked by a conducting gel. It has a large surface area with very low current density and returns the current from the patient to the surgical diathermy unit without heating or burning effects.

2. Bipolar Diathermy:

It consists of **two active electrodes** in the form of two limbs of a special forceps. The electrosurgical current flows through one side of the forceps, through the tissues and back through the other side of the forceps. The current is therefore localized to a small volume of tissue between the tips of the forceps (few millimeters). It is very useful for applications such as neurosurgery where it is necessary to localize the current and prevent excessive tissue damage.

There is **no need for the neutral patient's plate** (return electrode).

Although the hazards of the unipolar electrode are not present in the bipolar type, the cutting electrodes of the unipolar one are better than the bipolar one.

Complications and Hazards:

1. Diathermy Burn:

Hazards of burn occur **more with the monopolar type** when electrosurgical current flows through a cross section of tissue, small enough to result in a high current density that causes burning of tissue or coagulation of blood. This may occur in the following conditions:

- If the neutral plate is not correctly attached to the patient's skin where only a small surface area of the plate is attached to the patient's skin.
- If the neutral plate has a small surface area.
- If the pad covering the plate becomes dry.
- If the wire connecting the plate to the surgical diathermy unit is broken or disconnected.

In these conditions, the current may return to the electrosurgical unit through any point at which the patient touches an earthed metal object e.g.,

- When a patient's hand or even a patient's ring touches the metal of the operating table.
- ECG electrodes.
- Presence of any highly conducting materials such as metal implants or a ring which may make the current flow pass through them easier due to the low resistance of the metal compared to the surrounding tissues

These cause burns at the site of contact.

Recent diathermy units are capable of detecting poor contact between the return electrode and the patient by monitoring impedance and triggering the alarm if the return electrode is unplugged.

2. Pacemaker Dysfunction:

Surgical diathermy may cause **pacemaker failure**. The effect of surgical diathermy on pacemakers and the precautions are discussed in the chapter of "Cardiovascular Diseases".

3. Interference with Electronic Monitoring Devices:

This is less likely with modern surgical diathermy units.

4. Fire and Explosions:

This risk is decreased nowadays due to absence of inflammable anesthetic agents e.g., diethyl ether.

Defibrillator (Cardioverter), DC shock (Electric Cardioversion)

It is used either in elective or in emergency cases.

Mechanism of Action:

DC electrical discharge will pass via the heart causing:

- Simultaneous depolarization of all excitable myocardial cells.

- Interruption of abnormal pathways and foci.
- Prolongation of the refractory period.

Idea:

It contains a **capacitor** in which electric charges are stored until released in a controlled fashion. When the capacitor is set to discharge, it provides a single shock in the form of electric energy up to 360 joules. This energy reaches the heart in 2-4 milliseconds.

Direct current (DC) is more effective and less damaging to the heart than alternating current (AC) (figure 5-104).



Figure 5-104: A Defibrillator

Technique:

After **heavy sedation or light general anesthesia**, a DC defibrillator is applied by either self adhesive pads or reusable paddles.

- **Paddles' sizes** are 8-13 cm for an adult.
8 cm for a child.
4.5 cm for an infant.
- **Larger possible paddles are preferred** that can fit on the chest and not overlap to decrease any shock-induced myocardial necrosis by distributing the current over a wide area.
- **Placement of paddles** is either:
 - a. **Antero-laterally** with the patient in the supine position (**standard**):
 - One paddle is placed on the right 2nd intercostal space next to the sternum.
 - The other is placed on the left 5th intercostal space in the mid-clavicular line (i.e., **sternum and apex**).
 - Or b. **Antero-posteriorly** with the patient in the lateral position.
 - One paddle is placed on the left 5th intercostal space in the mid-clavicular line (**apex**).
 - The other paddle is placed posteriorly in the **left infra-scapular region**.

The paddles should not be placed over bones (scapula, sternum or vertebrae) or within 12 cm of a permanent pacemaker.

- The **skin** must be protected with electrolyte jelly, saline-soaked gauze or any type of conducting pads to
 - Prevent skin burns.
 - Decrease trans-thoracic impedance and so increase success rates.

Presence of excessive hairy skin makes the electrode contact with the skin suboptimal, resulting in air pockets between the defibrillator paddles and the skin from poor adhesion. Therefore, the pad area may need to be shaved (in addition to the jelly) to achieve good electrode contact.

- **Timing:** as the electrical current is impeded by passage through air, the defibrillator current should; therefore be delivered during expiration.

Synchronization:

- It is the timing of the delivery of the shock during the QRS complex **away from the T wave or ST segment** i.e., the synchronized DC shock is like the unsynchronized DC shock; if it is applied on a T wave, it may precipitate VF.
- A synchronized DC shock is needed in all tachyarrhythmias (as supraventricular tachycardia, atrial flutter, atrial fibrillation, or ventricular tachycardia with pulse).

- An unsynchronized DC shock is needed in ventricular tachycardia without pulse or ventricular fibrillation.

Energy Required:

The energy output should be kept to the minimal effective level to prevent myocardial damage, so start with the minimal energy.

➤ **Monophasic Defibrillators:** they produce a **monophasic waveform** where the electric current travels in one direction through the chest.

Regardless of the type of arrhythmia, a higher energy level is required when the 1st shock is ineffective; therefore, gradually increase the energy with 50-100 Joules increments as needed.

In VT and VF, 360 joule shock is required for adults by monophasic defibrillators.

➤ **Biphasic Defibrillators:** recent defibrillators produce a **biphasic waveform** where two consecutive pulses are produced i.e., the current travels first in one direction and then in the other. This enables defibrillation to occur with a lower energy than with the monophasic single pulse.

Arrhythmias	Adult (Joules)	Child (Joules/kg)
• Paroxysmal supraventricular tachycardia	25-50	0.5-1 J/kg
• Hemodynamically stable ventricular tachycardia (VT)	25-50	0.5-1 J/kg
• Atrial fibrillation	50-100	1-1.5 J/kg
• Hemodynamically unstable ventricular tachycardia	120-200	2 J/kg
• Ventricular fibrillation	120-200	2 J/kg

In VT and VF, **150-200 joule** shock for **adults** and children > 8 years of age.
50-75 joule shock for children < 8 years old.

N.B.:

- Higher energy levels may be needed in a patient with a thick thorax e.g., emphysema.
- Lower energy is needed if internal cardiac electrodes are used in patients with an open chest.
- An **automated external defibrillator (AED)** is now available. It is technologically advanced microprocessor-based device that can identify life-threatening arrhythmias and differentiate between shockable and nonshockable rhythms. It can deliver electric shock automatically. Para-medical personnel, not trained in defibrillation techniques, can use it for early and emergency defibrillation.
- An **automated implantable cardioverter defibrillator (AICD)** is now available. This is used for patients with recurrent life threatening arrhythmias. It can detect the arrhythmia and deliver DC shock automatically.

Precautions:

- If **ventricular arrhythmias** develop following the initial shock, lidocaine should be given before the next one.
- If the patient remains in VF after 3 attempts of DC shock, **cardiopulmonary resuscitation** should be continued and the shocks should be repeated after i.v. epinephrine.
- **Asystole** does not respond to DC shock, so it should be distinguished from VF by multiple ECG leads.
- **The place for performance of cardioversion in elective cases:**

Cardioversion should be done only in areas where a **full range of cardiopulmonary resuscitation tools** including drugs, cardiac pacing capabilities and airway management is available e.g., intensive care units, emergency rooms, or recovery rooms.

The indications of the pacemaker and the anesthetic management of elective cases undergoing cardioversion are discussed in the chapter of "Cardiovascular Diseases".

Cardiac Pacemakers

Definition:

It is an electronic device which can artificially pace the heart, so the myocardium will contract when stimulated.

Components: All pacemakers consist of:

1. Pulse Generator:

It consists of an energy source (battery) and electrical circuits necessary for pacing and sensing functions. The battery is outside the body in a temporary pacemaker and is inserted subcutaneously usually under the chest wall in a permanent one.

Electrical impulses are formed in the pulse generator and are transmitted to the endocardial or myocardial surface of the heart causing mechanical contraction (figure 5-105).



Figure 5-105: A Pacemaker generator; internal (left) and external (right)

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2. Pacing Electrode: for sensing and/or pacing.

The electrode is the exposed metal end in contact with the heart either from inside (i.e., endocardium) or from outside (epicardium or myocardium).

3. Pacing Lead:

It is an insulated wire which connects the electrode to the pulse generator.

Electrode Arrangement:

It is either a uni- or bipolar electrode system.

	Uni-polar Electrode System (figure 5-106)	Bi-polar Electrode System (figure 5-107)
	<p>Figure 5-106</p>	<p>Figure 5-107</p>
Components	<ul style="list-style-type: none"> - It has only one electrode inside the heart called the cathode (active, negative or stimulating) electrode. - Current flows from the cathode, stimulates the heart, and returns to the anode (ground or positive) electrode on the case of the pulse generator to complete the circuit. 	<ul style="list-style-type: none"> - It has 2 electrodes (cathode and anode), at a short distance from each other, at the distal end and both lie within the cardiac chamber being paced. - The tip electrode is usually the cathode while the proximal electrode is the anode.
N.B.	<ul style="list-style-type: none"> - With modern pacemakers, there is a little difference between the unipolar and bipolar electrode systems. Recently, there are multi-polar pacemakers with multiple connections. 	

Pacemaker Identification

• In 1970s, the **Intersociety commission of Heart Disease (ICHD)** suggested a classification code for cardiac pacemakers, which is now widely accepted.

The original nomenclature involved a 3-letter identification code:

The 1st letter of the code, signifies the chamber(s) paced.

The 2nd letter of the code, signifies the chamber(s) sensed.

The 3rd letter of the code, signifies the mode of response to a sensed P or R wave, either inhibited or triggered.

Examples:

VOO pacemaker: - It paces the ventricle (ventricular pacemaker).

- It has no sensing capability (it does not sense intrinsic R waves or P waves).

- It has no mode i.e., **asynchronous (fixed rate)**.

VVI pacemaker: - It paces the ventricle (ventricular pacemaker).

- It senses the ventricle (i.e., it senses intrinsic R waves).

- It is inhibited (i.e., when it senses intrinsic R waves, it inhibits the artificial pacing).

It is the **standard ventricular demand pacemaker**.

DVI pacemaker: - It paces both the atrium and ventricle.

- It senses the R wave of the ventricle.

- It is inhibited (i.e.,.....).

DDD pacemaker: - It paces both the atrium and ventricles.

- It senses both R waves of the ventricle and P waves of the atrium.

- It is triggered when it senses the P wave of atrial activity, then it is inhibited when it senses the R wave of ventricular activity after the preset atrio-ventricular interval i.e., **synchronized**.

• In 1980, this code was extended to 5 letters and was intended primarily for permanent pacemakers. The last 2 letters can be detected when not applicable.

North American Society of Pacing and Electro-physiology (NASPE)

and The British Pacing and Electro-Physiology Group (BPEG) Code:

NASPE/BPEG Generic Pacemaker Code:

1 st letter or position I	2 nd letter or position II	3 rd letter or position III	4 th letter or position IV	5 th letter or position V
Chamber (s) paced.	Chamber (s) sensed.	Response (s) of the generator to sensed P or R waves.	Programmable function of the generator.	Multi-site pacing (when 2 atria or 2 ventricles are paced).
O = None A = Atrium V = Ventricle D = Dual (V + A)	O = None (asynchronous) A = Atrium V = Ventricle D = Dual (V + A)	O = None (asynchronous) T = Triggered I = Inhibited D = Dual (T + I)	O = None (Fixed function) P = Programmable (rate and/or output) M = Multi-programmable C = Communicating R = Rate modulation	O = None A = Atrium V = Ventricle D = Dual (A + V)

(This code is widely used nowadays)

N.B.: Intersociety Commission of Heart Disease (ICHD) Code:

The same as NASPE/BPEG code except in the 5th letter or position V which represents the anti-tachyarrhythmia function of the generator.

O = None.

P = Pacing.

S = Shock.

D = Dual (P + S).

Types of Pacemakers

The types are shown in figure 5-108.

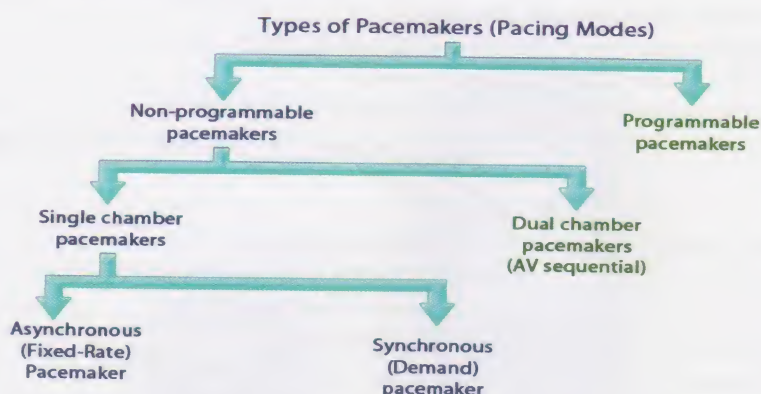


Figure 5-108: Types of pacemakers

1-Asynchronous (Fixed-Rate) Pacemakers:

They were the first type invented and they are the simplest. They discharge at a preset rate that is independent of the patient's heart rate (i.e., discharges at a **preset fixed rate** no matter what the patient's heart rate is). They can be atrial or ventricular. In the ICHD system, they are coded **AOO** or **VOO** respectively (figure 5-109).

Disadvantages:

- Waste energy.
- Normal rate competition (when the normal heart rate reappears).
- There is a chance (although remote) of causing ventricular fibrillation, if the pacemaker impulse occurs while the myocardium is repolarizing.

2- Synchronous (Demand) Pacemakers:

They have replaced the asynchronous type. They discharge at a preset-rate and pace the ventricle only when the spontaneous heart rate drops below the preset-rate. It can be either ventricular or atrial:

a) Ventricular Synchronous Pacemakers:

They are either triggered or inhibited (they act via a single electrode).

i- Ventricular-triggered pacemakers (VVT):

- If they sense an R wave, they emit an impulse into the absolute refractory period; therefore, they do not trigger another contraction.
- When the patient's heart rate is < the preset-rate, the generator paces the ventricle i.e., triggered to pace the ventricle.
- When the patient's heart rate is > the preset-rate, competition does not occur because the pacemaker impulses will be triggered to discharge into the QRS complex (absolute refractory period).
- Advantage: No competition.
- Disadvantage: Energy consuming.

ii- Ventricular-inhibited pacemakers (VVI):

- If they sense an R wave, then the generator impulse is stopped when the patient's heart rate is adequate (figure 5-110).

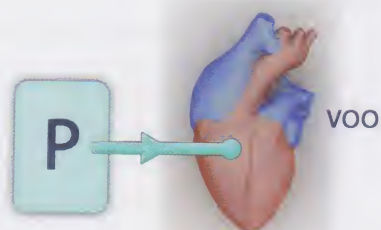


Figure 5-109: VOO mode

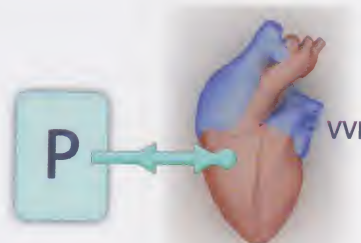


Figure 5-110: VVI mode

- When the patient's heart rate is $<$ the preset-rate, the generator paces the ventricle.
- They are the **most popular** type and the most common pacing mode is VVI.
- Advantages:
 - No competition.
 - Energy conservation.

b) Atrial Synchronous Pacemakers (VAI, VAT or VDD):

- They act via a bipolar electrode system.
- When the P wave is sensed, the generator impulse is stopped (VAI mode or P wave inhibited pacing) (figure 5-111).
- When the P wave is not sensed, the ventricle is paced at a preset-rate.

N.B.: Single chamber atrial pacing is used in patients with a slow sinus rate and intact atrio-ventricular (AV) conduction. It increases the cardiac output by 25% due to preserving atrial contraction.



Figure 5-111: VDD (left) and VAT (right) modes

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c) Dual Chamber (AV-Sequential) Pacemakers (DVI or DDD):

They are ideal because the atrial contribution to ventricular stroke volume is preserved.

Two electrodes are used, one in the atrial appendage and the other in the right ventricular apex (figure 5-112).

The most common pacing mode is DVI.

- If the pacemakers sense an R wave, the generator impulse is stopped (i.e., inhibited).
- When the patient's heart rate is $<$ the preset-rate, both the atrium and the ventricle are paced.
- The atrium is stimulated to contract 1st, then after an adjustable PR interval, the ventricle is stimulated to contract.
- These pacemakers are blind to atrial activity (i.e., they do not sense P waves) and atrial pacing may compete with the patient's own intrinsic atrial rhythm.



Figure 5-112: DDD (left) and DVI (right) modes

N.B.: Modes of pacemakers: In summary, they sense either:

- The P wave (i.e., atrial contraction): they are either:
 - **Triggered:** the pacemaker paces the ventricle when it senses the P wave. It is used when there is an A-V conduction block.
 - Or - **Inhibited:** the pacemaker is inhibited to pace when it senses the P wave. It is used when there is normal A-V conduction.
- The R wave (i.e. ventricular contraction): they are either:
 - **Triggered:** the pacemaker is triggered to pace when it senses the R wave. It paces in the absolute refractory period.
 - Or - **Inhibited:** the pacemaker is inhibited when it senses the R wave.

4- Programmable (Rate-Responsive or Rate-Adaptive) Pacemakers:

They have been widely used since 1980. The pacing rate, pulse duration, voltage output and R-wave sensitivity are the most common programmable functions. Recently, in modern pacemakers, refractory periods and PR intervals are also programmable.

Methods of Implantation of the Pacemaker:**A- Emergency and Temporary Pacing:****Indications:**• **For emergency pacing;**

- While preparing the patient for permanent pacing because it is easy to use.
- In cardiac arrest due to asystole (of choice).

• **For temporary pacing:**

- In a patient with LBBB who is undergoing central hemodynamic monitoring.
- For elective overdrive suppression of hemodynamically stable tachyarrhythmias.
- When other forms of pacing are not available.

Techniques: It is done by one of the following routes:

1- Transvenous (Endocardial) Pacing:

The two pacing electrodes are placed in one catheter which is inserted into a central vein down to the endocardial surface of the right ventricle under X-ray control. A subclavian, internal jugular (both are the most common because they provide better lead stability and greater patient freedom), brachial, femoral, external jugular or antecubital approach may be used.

2- External Transcutaneous Pacing:

It is simple and non-invasive as two large external skin electrodes (8 cm diameter) are placed; one on the cardiac apex, and the other on the manubrium or the right scapula.

3- Transesophageal Pacing:

It is replaced nowadays by transcutaneous pacing. It is non-invasive. The two pacing electrodes are introduced via the esophagus. It is incorporated into an esophageal stethoscope. Esophageal ECG may be added.

4- Transthoracic Pacing:

It is replaced nowadays by transcutaneous pacing.

A needle and stylet are inserted into the right ventricle either:

- To the left of the sternum at the level of the left 4th intercostal space (bare area of the heart).

Both the needle and stylet are directed perpendicular to the skin.

or - To the left of the xiphoid process with the needle and stylet directed inwards and upwards at an angle of 45° towards the left nipple.

The needle and stylet are connected to lead V of a standard electrocardiogram (ECG) monitor. If perforation of the right ventricle occurs, it will be indicated by an injury current on the ECG monitor (provided that there is no complete ventricular asystole).

B- Permanent or Long-Term Pacing:

The pacemaker is implanted in the abdominal wall, axilla or under the breast. The negative electrode is placed on the heart surface, and the positive electrode is incorporated into the implanted pacemaker. The pacemaker is small in size and its outer covering is made of biologically inert silicon material, which does not produce tissue reaction and is not rejected by the body. The pacemaker is battery-operated using a long-life battery, either mercury zinc type with an anticipated life of 3 years or lithium type with an anticipated life of 10 years.

Problems and Hazards of Pacemaker (and their Precautions):

1- Complications Related to the Placement of the Pacemaker: such as infection at the site of the insertion, thrombophlebitis, arterial puncture and hematoma, pneumothorax, hemothorax, or cardiac perforation and tamponade.

Therefore, insertion of the pacemaker should be done by an experienced physician under aseptic conditions especially with intravenous and trans-thoracic types.

2- Complications Related to the Electrode:

Electrode disconnection and dislodgement may occur especially with the transvenous endocardial leads due to muscle movement, mechanical ventilation, or pulmonary artery catheter. This leads to pacemaker failure.

Therefore, patient transposition and transportation must be done with care to avoid this complication. Some recent types of pulmonary artery catheter contain an intracardiac pacemaker lead.

5- Induction of Arrhythmias:

With the fixed rate pacemaker i.e., asynchronous, the pacing stimulus may occur during the vulnerable T-wave period and **induce ventricular fibrillation**. This risk is very rare because the output of the pacemaker is very small, except if there is a risk factor as acid-base or electrolyte disturbance, or hypoxia. Ventricular fibrillation may also be drug-induced due to digitalis toxicity or due to catecholamines.

Therefore, ECG monitor is essential if there is a risk of ventricular fibrillation.

6- Diaphragmatic or Skeletal Muscle Stimulation:

This occurs if the output from the pacemaker is large.

Therefore, the pacemaker output should be adjusted and decreased to avoid this problem.

7- Pacemaker Syndrome:

This is a physiologic disorder caused by a ventricular-inhibited pacemaker (VVI) implanted in a patient with intact ventriculo-atrial conduction, so a retrograde P wave or ventriculo-atrial conduction follows each paced QRS complex.

In some patients, this retrograde atrial conduction may decrease the cardiac output and cause systemic hypo-perfusion; therefore, vertigo, light headedness, syncope and hypotension may occur.

Therefore, DVI pacemaker may be used to avoid this problem.

8- Failure of the Demand Mechanism:

This occurs with demand pacemakers. The pacemaker may be suppressed if the patient's intrinsic rate exceeds the programmed rate.

Therefore, in this case, the heart rate can be slowed by drugs as edrophonium or maneuvers as carotid sinus massage or Valsalva, which increase vagal tone under ECG monitoring. If this fails, the pacemaker should be converted to asynchronous mode.

9- Microshock Hazard:

It usually occurs with temporary pacemaker especially if the contact points between the pulse generator and the pacemaker leads are not properly insulated.

Therefore, frequent checking of the pacemaker is needed.

10- Electromagnetic Interference:

The pacemaker may pick up electric signals from any source of electromagnetic interference close to the patient e.g., surgical diathermy, magnetic resonance imaging (MRI), cardioversion, defibrillator and microwave. This may shut off the unit or cause rapid pacing and ventricular fibrillation.

Therefore,

- Advise the patient to avoid the electromagnetic sources as microwave oven, electric razor, telephone transformer, or high voltage power transmission lines.

- Magnetic resonance imaging (MRI) is **absolutely contraindicated** by most generator manufacturers as deaths have been reported because it causes pacing inhibition or rapid pacing.

If MRI is absolutely indicated, the pacemaker should be programmed to its lowest voltage output or pulse width or to OOO mode (provided that the patient has an adequate underlying rhythm).

- Precautions with diathermy are discussed in the chapter of "Cardiovascular Diseases".

- During intraoperative use of defibrillators e.g., for ventricular fibrillation (VF), take care of the following:

- The paddles should not be placed directly over the pulse generator.
- An acute increase in the stimulation threshold may follow external defibrillation which may cause loss of capture and need prompt insertion of a transvenous pacemaker.
- They may cause **endocardial burns and fibrosis** at the electrode-endocardial interface. So, increase the stimulation threshold and emphasize the need to administer the lowest effective dose of electrical energy by the defibrillator as possible.
- The pacemaker function should be checked following defibrillation.

Nowadays: - Good shielded pacemakers are available.

- New pacemakers are now designed such that external electrical fields will change the pacemaker rhythm to an asynchronous mode rather than shut off the unit or cause VF.

11- Myopotential Interference:

It can cause inhibition of the pacemaker generator because they are falsely interpreted by the pacemaker as intrinsic R waves. This occurs with the types which sense the ventricles.

For examples, - fasciculations of succinylcholine,

- myoclonus action of etomidate,
- postoperative shivering,
- and - seizures.

Therefore, this problem can be prevented by reprogramming the pacemaker to an asynchronous mode or decreasing R wave sensitivity.

10- Battery Failure:

This causes loss of the pacing function of the pacemaker.

Therefore, battery checking is important. Modern batteries may last up to 5-9 years

11- Related to traction:

Sometimes, it is necessary to remove the pacing electrode due to malfunction. The majority can be pulled out by gentle traction, but sometimes the pacemaker becomes adherent to the cardiac muscle. This may necessitate forceful prolonged traction which can cause:

- Arrhythmias as ventricular tachycardia or fibrillation.
- Shock due to invagination of the right ventricular wall into the tricuspid valve.
- Tear of the right side of the heart.

Indications, anesthetic management of a patient with a permanent pacemaker undergoing surgery, and anesthetic management for implantation of a pacemaker are discussed in the chapter of "Cardiovascular Diseases".

Automatic Implantable Cardioverter Defibrillator (AICD)

It was approved by the FDA in 1985.

Components:

AICD is usually combined with a pacemaker in the device. AICD is an automatic, diagnostic and therapeutic system. It is capable of sensing the rate and morphology of the ventricular rhythm, detecting ventricular tachycardia or fibrillation (diagnostic system) and terminating of VT or VF (therapeutic system).

It consists of a **pulse generator** containing **capacitors, batteries, several leads and titanium case**. The leads are either:

- a. Sensing leads: - transvenous bipolar leads placed in the right ventricular apex,
or - two-myocardial leads placed on the left ventricle.
- or b. Defibrillating leads: - two epicardial or pericardial patches,
or - a transvenous spring electrode positioned at the junction of superior vena cava and right atrium with the epicardial patch placed on the right ventricle (figure 5-113).



Figure 5-113: An AICD

NASPE/BPEG Generic Defibrillator Code (NBD):

Like pacemakers, AICDs have a generic code which indicates lead placement and function.

Position or Letter 1	Position or Letter 2	Position or Letter 3	Position or Letter 4
Shock chamber(s)	Anti-tachycardia pacing chamber(s)	Tachycardia detection	Anti-bradycardia pacing chamber(s)
O = None A = Atrium V = Ventricle D = Dual (A + V)	O = None A = Atrium V = Ventricle D = Dual (A + V)	E = Electrogram H = Hemodynamic (not yet available)	O = None A = Atrium V = Ventricle D = Dual (A + V)

Principles of Action:

The Sensing System identifies:

1- The morphology of the ventricular rhythm through a **morphology mode** called the **probability density function (PDF) criterion** i.e., morphology **waveform analysis with comparison to stored templates**. PDF must be programmed so that the device will not shock a relatively rapid sinus rhythm.

2- The rate of the ventricular rhythm through a **rate mode**, as the AICDs can measure essentially each cardiac RR interval and then recognize the rate.

To recognize VT, the sensing system requires a minimum of 8 fast cardiac beats of characteristic morphology.

3- **Stability criteria:** The PR interval of VT is usually relatively constant, whereas the PR interval of AF with a rapid ventricular response is quite variable.

4- **QRS width criteria:** QRS in VT is usually wide (> 120 m sec), whereas in supraventricular tachycardia (SVT) it is narrow (< 110 m sec). Supraventricular tachycardia is the most common etiology of inappropriate shock therapy.

5- **Intelligence:** In dual chamber devices, an attempt to associate atrial activity to ventricular activity is performed.

The Therapeutic System (the Response):

- The response of AICD may be one of the following actions:
 - **Shock with a high energy to cardiovert or defibrillate the heart.**
 - **Anti-tachycardia shock with lower energy** when enough short PR intervals are detected.
 - **Anti-bradycardia shock** (developed since 1997) when enough long PR intervals are detected.
- If the criteria of an arrhythmia are met and the arrhythmia is recognized, the system is delayed for 2.5 seconds to ensure that the arrhythmia is sustained.
- If the arrhythmia is sustained, the pulse generator charges its capacitors and discharges the 1st programmed shock. This takes a total of $\approx 8-14$ seconds (figure 5-114).
- If the arrhythmia is persistent, the pulse generator will discharge 4-6 up to 18 more shocks per event, each at 30 Joules. Before each shock, the pulse generator takes 10-25 seconds to reevaluate the arrhythmia.

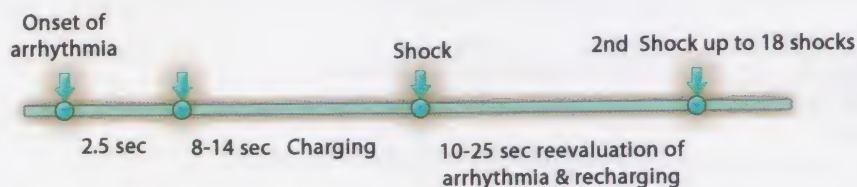


Figure 5-114: The response of AICD

Potential Problems with AICD Function:

A) Problems with Programmable Parameters:

1- The morphology mode (probability density function):

Some non-malignant ventricular rhythms and asymptomatic non-sustained VT may have unusual morphologies and trigger the AICD (by meeting both the PDF and rate criteria) causing false discharge.

2- The rate mode:

In AICD devices that detect only the heart rate, they are commonly initiated by sinus or supraventricular tachyarrhythmias, whose rate exceeds the programmed preset cut off rate of the device, causing false discharge of the AICD.

These false discharges of the AICD may cause premature battery depletion.

To solve both of these problems:

- Set the programmable cutoff rate of the device at a higher rate than the maximum sinus rate of the patient during exercise and lower than the patient's VT rate.
- If the patient has multiple VT, the cutoff rate of the device should be set to treat the lowest VT and when this is done, the morphology mode of the device must be programmed so that the device will not counter-shock a relatively rapid supraventricular tachyarrhythmia.

Despite these efforts, some non-malignant ventricular rhythms and asymptomatic non-sustained VTs may trigger the AICD.

B) Electromagnetic Interference (Effect of Electrocautery):

- **False discharge** of the AICD can occur with **electrocautery** or other electrical signals from surgical equipment because the AICD may interpret the electrical signals as ventricular fibrillation.
- It has been reported that electrocautery has **initiated a counter-shock sequence** by the AICD which causes VT.

Precautions with Electrocautery:

- It is necessary to **deactivate the AICD device with a ring magnet**, but actually the effect of magnet application, like pacemakers, gives **unpredictable effects with AICD** such as:
 - Most AICD devices will temporarily suspend tachyarrhythmia detection (and therefore therapy).
 - Some other devices can be permanently disabled by magnet placement for > 30 seconds.
 - Generally, **most devices are not affected**.
- The same precautions taken with the pacemaker are applied with AICD.

C) Permanent Pacemakers:

a- Uni-polar pacemakers: they are **contraindicated** in patients requiring AICD because they interact with the sensing function of the AICD. During arrhythmia, the sensing lead of the AICD may sense the pacing artifact of the pacemaker as an R-wave (i.e., as the patient's real rhythm). This prevents AICD from being activated. If the pacemaker becomes in the asynchronous mode (fixed-rate mode), the sensing lead of the AICD will pick up 2 asynchronous beats, and this may cause the AICD to discharge unnecessary counter-shocks.

b- Bi-polar pacemakers: they do not affect AICD.

Indications, anesthetic management of a patient undergoing placement of AICD and anesthetic management of a patient with an AICD are discussed in the chapter of "Cardiovascular Diseases".

PART 12: NUCLEAR PHYSICS**Atoms**

An atom consists of a central nucleus containing protons and neutrons surrounded by orbiting electrons.

- **Protons:** They have positive charges.

The mass of a proton is 1840 times that of an electron.

The type of the atom i.e., element, is determined by the number of protons (the atomic number).

- **Neutrons:** They have no charges i.e., neutral.

The mass of a neutron is the same mass as that of a proton.

The stability of the nucleus i.e., isotopes is determined by the number of neutrons.

- **Electrons:** They have negative charges.

The mass of an electron is 1/1840 that of a proton.

The ions are determined by gaining or losing electrons.

In any atom, the number of protons always equals the number of electrons; therefore, the atom is electrically neutral, for example,

- hydrogen has one proton in the nucleus and one orbital electron (it is the simplest atom),
- helium has 2 protons,
- carbon has 6 protons.

Atomic number: is the number of protons.

Mass number: is the number of protons + neutrons

Atomic weight: is the weight of an atom relative to that of oxygen atom (which is 16) (figure 5-115).

Ions

Any atom may gain or lose one or more electrons and become negatively or positively charged and is then known as an ion.

In an electric field, a positively charged ion moves towards the cathode and is called **cation** (cathode ion) and a negatively charged ion moves towards the anode and is called **anion** (anode ion).

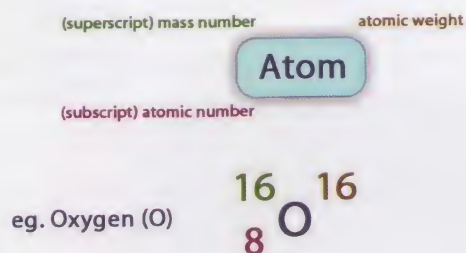


Figure 5-115: Oxygen atom

Isotopes (Nuclides)

These are elements having the same atomic number (i.e., the same number of protons), but different mass number (i.e., different numbers of neutrons). This means that for a particular element with a given number of protons, there are different isotopes with different number of neutrons.

Examples of isotopes (figure 5-116):

- Hydrogen; hydrogen-1 i.e., contains one proton and there is no neutron.
hydrogen-2 (deuterium) i.e., contains one proton and one neutron.
hydrogen-3 (tritium) i.e., contains one proton and there are 2 neutrons.
- Carbon; carbon-12 i.e., contains 6 protons and 6 neutrons.
carbon-14 i.e., contains 6 protons and 8 neutrons.

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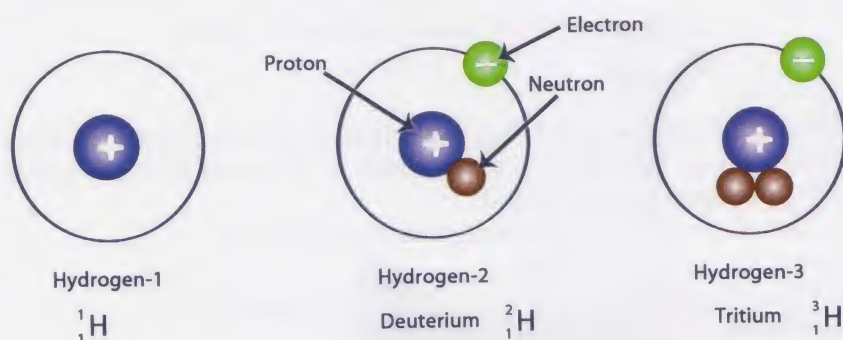


Figure 5-116: Isotopes of hydrogen

Many isotopes of elements occur naturally, but others may be produced artificially in a nuclear reactor.

Types of Isotopes:

- Stable** i.e., their nuclei do not disintegrate e.g., hydrogen-1 and hydrogen-2 (deuterium).
- They are not radioactive and are difficult to isolate or detect. They can be identified by the mass spectrometer.
- They have few special uses in medicine.
- Unstable** i.e., their nuclei disintegrate and will not hold together indefinitely and emit radiations e.g., hydrogen-3 (tritium). They are called **radioactive isotopes (radioisotopes)** or **radionuclides**. The unstable nuclei will continue to eject (emit) particles until a stable isotope is obtained.

N.B.: **Radioactivity**: is the ability to emit radiations.

The unstable nucleus of a radioactive isotope, due to its disintegration and emission of radiations, eventually changes into another element.

Radioactive Decay:

It is the process of one element changing into another. It may occur in one of the following ways:

- The nucleus may **emit beta (β) particles**. They are either negative charged electrons or positively charged positrons.
- The nucleus may **capture** one of the **electrons** surrounding it.
- The nucleus may **emit alpha (α) particles**. They are a combination of two protons and two neutrons i.e., a **helium-4 nucleus**.
- The nucleus may undergo spontaneous **fission i.e., splitting** into several fragments.

After a nucleus has decayed by one of these processes, it is usual for the nucleus of the new element formed to emit one or more **gamma (γ) rays**.

- A gamma ray is not a particle but an electromagnetic wave. However, because it has a high frequency and short wavelength, and is emitted as packets of energy called photons, it behaves in many respects like a particle.

N.B.: **Metastable State:**

If there is a delay between the decay of the nucleus and the emission of the associated gamma rays, the nucleus is said to be in a metastable state until the gamma rays have been emitted. The metastable state has its own rate of decay to a more stable form or half-life. The metastable isotope is identified by an "m" after the mass number e.g., technetium-99m decays to Tc-99 with half-life 6 hours.

An **example** of radioactive decay is the **tritium**. One of the neutrons in the nucleus of the tritium changes into a proton and an electron; this electron is ejected from the nucleus. The nucleus then contains 2 protons and one neutron, and the atom of tritium has changed into an atom of the stable element helium-3 (figure 5-117).

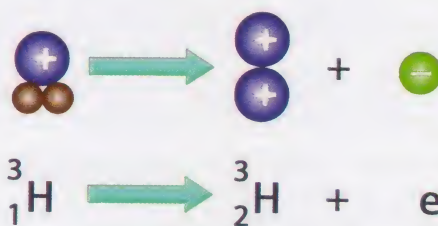


Figure 5-117: Radioactive decay of tritium

Units of Radioactivity:

The SI unit of radioactivity is the **becquerel (Bq)** which is equal to one disintegration per second.

In the past, radioactivity was measured in **curie** which is the quantity of any radioactive substance undergoing 3.7×10^{10} disintegrations per second.

One curie (Ci) = 3.7×10^{10} disintegrations per second.

Therefore, one curie (Ci) = 3.7×10^{10} Bq

Duration of Radioactivity (Half-Life):

The rate of radioactive decay is measured by the half-life.

Physical half-life (T_p): is the time required for half the radioactive atoms present to disintegrate and decay. Similarly, in the next half-life, half of the remaining atoms will decay.

Biological half-life (T_b): is the time taken by the body to reduce, by elimination and excretion, the amount of radioactivity to half.

Effective half-life (T_e): combines both the physical half-life and biological half-life i.e., the half-life due to natural decay and excretion from the body. It is less than each of them.

$$\frac{1}{T_e} = \frac{1}{T_p} + \frac{1}{T_b}$$

For example; chromium-51 used in red cell volume measurement has a half-life of 27.8 days. Thus, if there are initially 10^{12} atoms of chromium-51 in a sample, there will be 5×10^{11} remaining after 27.8 days. After further 27.8 days, there will be 2.5×10^{11} atoms of isotope remaining, and so on.

Detection of Radiation:

1- Geiger-Muller Counter: for detection of beta particles.

The counter contains an inert gas (argon or helium) which becomes ionized by beta particles (electrons) producing an electric signal proportional to the number of particles. The signal is then amplified and displayed on a meter.

2- Scintillation Counter (Gamma Camera): for detection of gamma rays.

The counter contains a sodium iodide crystal, which produces small flashes of light (scintillations) when it absorbs the energy of gamma rays. These flashes are converted into an electrical pulse and amplified by a photomultiplier tube, and then displayed on a meter (figure 5-118).

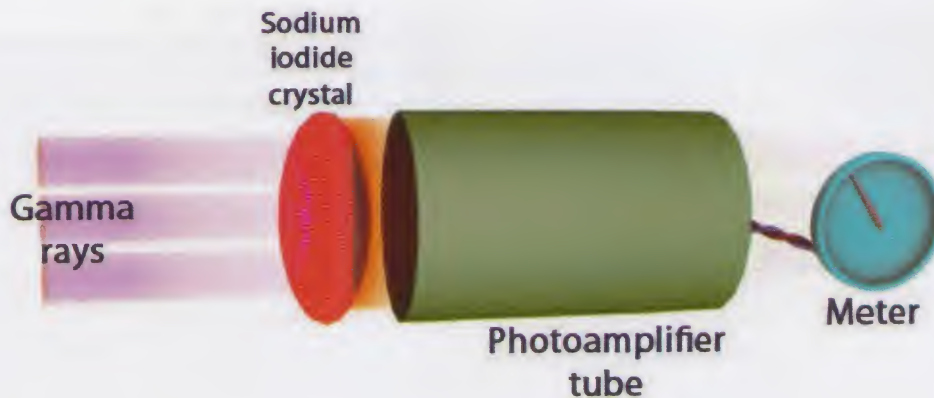


Figure 5-118: Scintillation counter

N.B.: X-rays:

- They are produced when a beam of electrons is accelerated from a cathode to strike an anode, usually of tungsten. A divergent beam of x-rays is produced, and a lead shield with a window is used to restrict the size of the beam (figure 5-119).
- X-rays are used for imaging purposes and in treatment of certain diseases.

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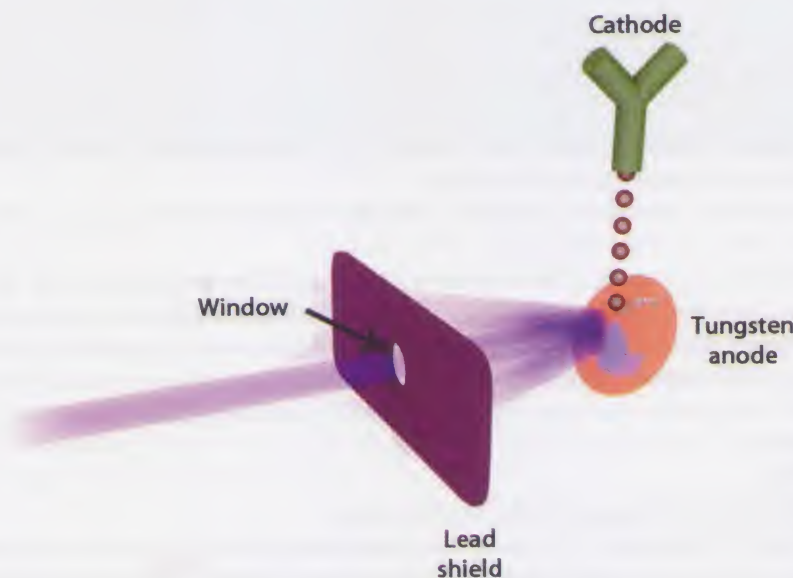


Figure 5-119: Production of x-rays

Ionizing Radiation

Types: Radiation is the emission of energy in the form of:

- Electromagnetic radiation: **X-ray** and **gamma ray**.
- Charged particles; **alpha particles** and **beta particles**.

All have the common property of **producing ionization within biological tissues**.

They have high energy content and are capable of producing electrically charged particles (ions) in the medium through which they pass. Their high energy causes ejection of electrons from some atomic orbits and in turn, the ejected electrons are deposited into other atomic orbits. Atoms which lose electrons, become positively charged ions, and those which gain electrons become negatively charged ions.

Therefore, in the therapeutic purposes, the energy of ionizing radiations is dissipated and absorbed in the tissues causing local tissue damage while in diagnostic radiology, the amount of energy absorbed is too small to cause any harmful biological effect.

Physical Properties: of ionizing radiations are shown in the following table:

Radiation	Source	Nature	Electric Charge	Velocity (km/s)	When emitted outside the body of the patient (i.e. penetrability)	When emitted inside the body of the patient
X-ray	from x-ray tube	Electro-magnetic radiation	Uncharged	300,000	They have very high penetration to the skin and deeper tissues.	
Gamma (γ) rays	During the decay of radio-active isotopes	Electro-magnetic radiation	Uncharged	300,000	They have very high penetration to the skin and deeper tissues.	a proportion of the radiation is absorbed by the tissues causing local tissue damage while the other proportion escapes from the body and can be measured externally by a suitable detector.
Beta (β) particles	During the decay of radio-active isotopes	Electrons or positrons	Negatively charged Positively charged	300,000	They have moderate penetration	all their energy is absorbed by the tissues causing local tissue damage, and they are not detected externally.
Alpha (α) particles	During the decay of radio-active isotopes	Combination of two protons and two neutrons i.e., a helium-4 nucleus.	Positively charged	20,000	they have the least penetration	

Biological Effects of Ionizing Radiations:

Ionizing radiation produces chemical changes in cellular components resulting in tissue damage. These biological effects are dose and time dependant. They include:

1- **Cellular effects:** ionizing radiation interferes with normal DNA synthesis and **mitosis** (somatic cell division) leading to chromosomal abnormalities. These effects are partly due to ionization and partly to the **formation of oxygen free radicals**, which are highly reactive and potentially cytotoxic. Tissues with **rapidly developing cells (rapid turnover)** are more affected by ionizing radiation e.g., bone marrow (pancytopenia), skin (erythema and hair loss), mucosa of gastrointestinal tract (bleeding and diarrhea), and gonads (sterility).

2- **Whole body effects:**

a- Early: Acute Radiation Syndrome (Radiation Sickness):

Early radiation injury is characterized by an acute (prodromal) phase and a subacute phase separated by a latent period of 1-3 weeks, during which time the patient may be completely asymptomatic.

The severity of acute radiation injury is determined by the dose and the time of exposure:

- **Exposure to < 150 cGy** (1 gray "Gy" = 100 rads and 1 rad = 1 cGy) produces minimal or no acute prodromal symptoms. Then after a latent period of 3-4 weeks, bone marrow depression occurs with reduction of platelets, granulocytes, and lymphocytes.
- **Exposure to 150-400 cGy** produces transient **nausea and vomiting** 1-4 hours following exposure. After a latent period of 1-3 weeks, **gastrointestinal symptoms (nausea, vomiting, and bloody diarrhea)** and **bone marrow depression (anemia, coagulopathy, and depressed immune function)** occur.
- **Exposure to 600-1000 cGy** produces **severe gastrointestinal symptoms** in the acute phase that may be life-threatening. Severe hematological complications can be expected to develop in survivors.
- **Prolonged exposure to high doses** produces a fulminating course with severe vomiting, diarrhea, tenesmus, dehydration, and **circulatory collapse**. **Neurological complications** may occur including ataxia, incoordination, weakness, confusion, seizures, and coma. **Death** occurs within 48 hours.

b- Late: carcinogenic and genetic effects.

Radiation Safety and Protection:

There are 3 sources of radiation during procedures:

- 1- Direct radiation from the x-ray tube.
 - 2- Leakage (through the collimators; protective shielding).
 - 3- Scattered (reflected from the patient and the area surrounding the body part to be imaged).
- Safety precautions include **minimal exposure to ionizing radiation**. This is known as the **ALARA principle**. ALARA is an abbreviation for "As Low As Reasonably Achievable" which refers to achieving the lowest radiation exposure possible to patients and health care workers.
 - An individual may wear a **photographic film badge** to monitor the total radiation dose received. The film badge contains a small piece of photographic film behind several different filters and permits estimation of the energy and dose of radiation received.
 - The main principle of radiological protection is time, distance, dose of exposure, and shielding:
 - **Time:** minimize the exposure time.
 - **Distance:** maximize the distance between oneself and the source of radiation. This is particularly effective since radiation exposure varies inversely with the square of distance from the radiation source (inverse square law).
 - **Dose of exposure:** digital subtraction angiography delivers considerably more radiation than fluoroscopy.
 - **Shielding:** by the usage of protective shielding as follows:
 - 1- **Appropriate handling** of radioactive isotopes e.g., wearing of **gloves** by people handling the material.
 - 2- **Appropriate storage** of radioactive isotopes e.g., by enclosing radioactive sources in **containers** made of a material that **absorbs radiation**.
 - 3- **Reduction of exposure to the external radiation.**
 - The ionizing radiations differ in the ability to travel through the air:
 - **Alpha particles:** travel only a **few centimeters** in air before their energy is expended and therefore the main problem is to ensure that **no** alpha-emitted material is inadvertently **inhaled or ingested**. Therefore, they should be kept in shielding containers.
 - **Beta particles:** travel a **few meters** in air before they are absorbed; therefore, **shielding** with radiation-absorbing material is necessary. The shielding material should be of **low density**, such as Perspex, because beta particles energy is converted **into x-rays** if they are decelerated rapidly by a high density material.
 - **Gamma rays:** travel **large distances** in air; therefore, **shielding** with **high dense** materials is necessary such as **lead**. A thickness of 7-cm lead will absorb at least 90% of gamma rays.
 - **X-rays:** travel **large distance** in air; therefore, **shielding** with **lead** is also needed either:
 - **Lead aprons** worn by staff exposed to radiation are necessary. A standard lead apron can reduce radiation exposure by 95%.
 - **Local lead shielding** used by the patients to protect parts of the body outside the main X-ray beam when radiographs are being taken.

N.B.:

- As actively dividing cells are particularly affected by ionizing radiations, **the fetus** is the most sensitive to the effect of radiation especially during the period of organogenesis in the first trimester of pregnancy. The adverse effects include mal-formations, growth retardation, and possible carcinogenesis. The fetus is at special risk even before the mother realizes that she is pregnant. Therefore, it is recommended that:
 - Women of reproductive capacity should be X-rayed only in the first 10 days of their menstrual cycle i.e., before ovulation has occurred (the 10-day rule).
 - Exposure of pregnant women to ionizing radiation should be kept to a minimum. A diagnostic examination such as ultrasound is safer and should replace radiological examination whenever possible.
- The symbol shown in figure 5-120 is displayed when there is a risk of exposure to ionizing radiation.

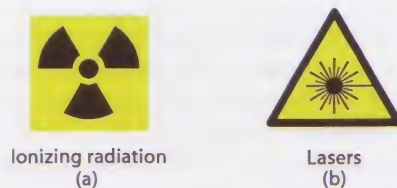


Figure 5-120: Warning symbols for ionizing radiation (left) and lasers (right); black with a yellow background

Clinical Applications of Radioisotopes (Radionuclides, Radiopharmaceuticals)

Radiopharmaceuticals are isotopes that are used in the nuclear medicine.

A) Therapeutic Uses:

1- Radiotherapy of Cancer:

Only radionuclides that emit alpha or beta particles are useful for radiotherapy. These particles lose all their energy to their surroundings over a very short distance from their origin and this energy is sufficient to kill cells. Actively dividing cells, such as tumor cells are particularly vulnerable.

The radiation may be given by either:

An external source: where the radiations penetrate the body from outside, for example,

- In the past, cobalt-60, which has a half-life of 5.3 years, was used.
- Nowadays, gamma rays are generated externally by means of a linear accelerator.

An internal source: where the radiation source is placed inside the body. It is either:

a) A sealed source: for example,

- A sealed yttrium-90 implant is used in the treatment of pituitary tumors which have caused acromegaly.
- A sealed caesium-137 capsule is implanted in the uterus in the treatment of some uterine tumors.

b) An unsealed source: for example,

- Caesium-137 is used with an 'after loading' technique, where cannulas are first placed in a tumor (e.g., of breast) and, once in position, caesium-137 needles are inserted down the cannulas to provide a high localized dose of radiation.
- Iodine-131 is selectively taken up by the thyroid gland which can be used in the treatment of thyroid tumors.
- Iodine-131 meta-iodobenzyleguanidine (MIBG) is used in the treatment of malignant pheochromocytomas.

2- Treatment of Other Conditions: for example,

- The use of oral iodine-131 in the treatment of thyrotoxicosis.
- The use of intravenous phosphorus-32 in the treatment of polycythemia rubra vera.

B) Diagnostic Uses:

They are divided into imaging and non-imaging techniques;

1- Imaging Techniques:

They utilize gamma ray-emitting isotopes. An image of the distribution of a radioactive isotope within the body or the organ to be studied is obtained by using a scintillation counter or gamma camera placed over the organ studied.

The isotopes commonly used for imaging techniques are technetium-99m, xenon-133, iodine-131, and krypton-81m because:

- They are easily attached to various chemical compounds which can be injected into the patient and taken up by the organ of interest so that the activity of the organ could be viewed e.g. technetium-99m pertechnetate or serum human albumin.
- They have a short half-life e.g., half-life of technetium-99m is 6 hours, thus reducing the radiation dose to the patient.
- They produce gamma rays of energy suitable for forming a good image.

For example:

- **Technetium-99m (Tc-99m):** is used for imaging **blood flow, thyroid, lung, brain, liver, bone, renal, and cardiac scans.**

Assessment of **cardiac** function (radioisotope angio-cardiography) can give information about intra-cardiac shunts, congenital defects, regional ventricular function, myocardial blood flow, and left ventricular ejection fraction.

- **Thallium-201:** is used to detect poor **myocardial blood supply** and scarring i.e., an infarct.
- **Xenon-133 inhalation:** is used for imaging the **lungs** (to study regional pulmonary ventilation/perfusion matching) and imaging the **brain** (to study regional cerebral blood flow).
- **Iodine-125 or -131 labelled fibrinogen:** is used to detect **deep venous thrombosis (DVT)**. When it is injected intravenously, it accumulates in the clot where it is detected by a scintillation counter. In this test, it is necessary to block the uptake of radioactive iodine by the thyroid gland by giving the patient a large dose of potassium iodide before the test is done.
- Positron emission tomography (see later).

2 Non-Imaging Techniques: (sometimes it is referred to as **nuclear pathology**)

• Measurement of body fluid compartments:

- **Tritium (hydrogen-3)-labelled water** is used for total body water measurement.
- **Chromium-51 labelled albumin** is used for **plasma volume** measurement.
- **Chromium-51 labelled red cells** is used for **red cell volume** measurement.
- **Carbon-14 labelled radioactive inulin** is used for **extracellular fluid volume** measurement.

In them, a small known quantity of the radioactive compound is injected and after a suitable interval, the dilution of the radioactive tracer in the patient's blood or extracellular compartment is measured, and plasma volume, red cell, or extracellular volume can be calculated.

• Measurement of cardiac output by:

- **Iodine-123 or -131 labelled serum albumin**, where it replaces the indocyanine green dye in the indicator dilution method.

• Measurement of blood flow to different organs:

Suppose an organ contains a given amount of a radioisotope at a particular time, the rate at which the radioactivity decreases in the organ depends on the blood flow and the volume perfused by this flow. A plot of radioactivity against time is a washout curve, from which the time constant and thus the blood flow may be determined.

• Study of drug metabolism: as;

- **Carbon-14 labelled anesthetic agent** is used to investigate the uptake of anesthetic agents in experimental animals, as it is inspired by the animal. The animal is then sacrificed and sectioned. The sections are placed in contact with a photographic film and, after development, the film is found to be darkened in areas due to exposure to radiation from the carbon-14.
- **Carbon-14 labelled muscle relaxants** are used to study the uptake of muscle relaxants.

• Radioimmunoassay (see later).

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Positron Emission Tomography (PET)

It is one of the clinical applications of radioisotopes. It is an imaging technique.

Idea:

• Some isotopes emit particles called positrons. **Positron-emitting isotopes** include:

- **Carbon-11** (its half-life is 20 min).
- **Nitrogen-13** (its half-life is 10 min).
- **Oxygen-15** (its half-life is 2 min).
- **Fluorine-18** (its half-life is 110 min).

• A **positron** has the same mass as an electron but with a positive charge. Therefore, positrons are also called positive electrons or anti-electrons. All positron emitters are produced by a cyclotron and generally have very short half-lives (as above); therefore, the investigations can be only performed close to a cyclotron, which must also have staff and facilities for sophisticated radiochemistry.

• Positrons collide with electrons producing **gamma rays**, which can be detected and displayed on a screen. Such gamma rays are not easily attenuated in tissues, with consequent superior image retention.

• It is expensive and not readily available.

Clinical Application:

PET is used to **localize and measure the metabolic rate** of any substance labelled with a positron-emitting isotope i.e., it is a **functional study**. If the organ under investigation is not working, no image can be obtained. For example,

• **Measurement of cerebral blood flow:** Since cerebral blood flow is coupled to brain metabolism, local uptake of **2-deoxyglucose labelled with any positron-emitting isotope** (usually **fluorine-18**) is a good index of regional cerebral blood flow. The concentration of isotope in any part of the brain can be monitored by PET scanning through the intact skull. Increased fluorine-18 labelled 2-deoxyglucose uptake in regions with reduced perfusion indicates the presence of viable brain tissues although there is reduced flow. N.B.: Glucose is not used because it is rapidly metabolized and enters glycolysis and glycogen synthesis, so it does not allow accumulation and detection of the isotope. Therefore, its analogue 2-deoxyglucose is preferred because it is slowly metabolized.

• Measurement of coronary blood flow:

Also, fluorine-18 labelled 2-deoxyglucose is used with the same idea as above. It can differentiate between viable myocardium with reduced flow (i.e., hibernation) which takes the isotope and dead myocardium with reduced flow (i.e., infarction) which does not take the isotope.

Radioimmunoassay

It is one of the clinical applications of radioisotopes. It is a non-imaging technique.

Idea:

- It is the ability to estimate **accurately** and **specifically**, even very small amounts, of certain hormones, drugs, and other substances by the techniques of competitive binding assays using radioactive isotope particularly **iodine-125**.
- When a labelled peptide (*A) e.g., iodine-125 labelled insulin is mixed with an antiserum antibody (anti-A) and both are mixed with the patient's serum containing the unlabelled peptide (A) e.g., endogenous insulin, the binding of the labelled peptide (*A) and the antibody (anti-A) is decreased when the endogenous peptide (A) is increased. The *A anti-A amount can be measured by counting radioactivity after suitable separation.

$$(*A) + (\text{anti-A}) + A = [*A \text{ anti-A}] + [A \text{ anti-A}]$$

The amounts of [*A anti-A] and [A anti-A] will be inversely related.

Clinical Application:

It can assess **hormones** (e.g., insulin, thyroxin, tri-iodo-thyroxin, estrogen, progesterone, and renin), **drugs** (e.g., digoxin, gentamycin, morphine) and **other substances** (enzymes, peptides, protein) **in the blood stream**.

N.B.: Non-Ionizing Radiation

It is radiation which arises from other parts of the electromagnetic spectrum (rather than X-rays and gamma rays). It dissipates its energy in tissues without producing ionization of these tissues like ionizing radiation, and therefore it is known as nonionizing radiation.

Types: they include:

- Radio waves.
- Visible light.
- Microwaves.
- Infrared waves.
- Ultraviolet waves.

They will be discussed in the next part.

PART 13: WAVE PATTERNS

In medicine, there are various biological processes that occur in a repetitive manner e.g., the ventilation of the lungs, the cardiac cycle and cerebral electrical activity. When these are monitored, a complex wave pattern is produced e.g., electrocardiogram (ECG), and electroencephalogram (EEG).

There are different types of simple waveforms (figure 5-121):



Figure 5-121: Wave patterns

- **The sine wave:** It is the most important because it is possible to produce any of the other patterns of waves by combining various different sine waves together.
- The saw-tooth wave.
- The square wave.

Wave motion is also present as:

- Variation in pressure in the case of sound waves.
- and • Vibration in the electric and magnetic fields in case of electromagnetic radiation such as light.

Characteristics of a sine wave

1- Phase:

It is the different angles of the wave along the horizontal axis (figure 5-122).

If two sine wave motions are compared, the relative displacement of one wave with respect to the other can be referred to in terms of the number of degrees by which the two waves differ along the horizontal axis (figure 5-123).

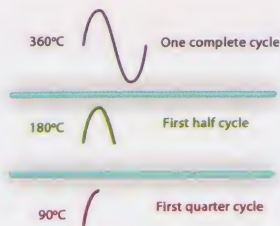


Figure 5-122: Phase of a sine wave

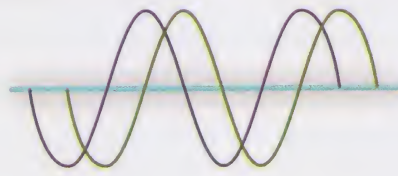


Figure 5-123: The two sine waves are 90° out of phase

5- Wavelength and Amplitude:

- **The wavelength** is the distance between any two corresponding points in two successive cycles i.e., the distance between two peaks or two troughs, or the distance between two points where the wave motion crosses the horizontal axis in the same direction.
- **The amplitude** is the maximum displacement of the wave from the horizontal axis in the same direction (Figure 5-124).

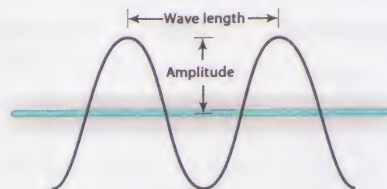


Figure 5-124: Wavelength and amplitude

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5- Frequency, Period, and Velocity:

- **The frequency of a wave** is the number of complete cycles which occur in 1 second, and in the SI system the unit of measurement for cycles per second is called **hertz (Hz)**.
- **The period of a wave** is the time taken for one complete cycle to occur.

It is the reciprocal of the frequency $T = \frac{1}{f}$ where T is the period and f is the frequency.

e.g., if the waveform has a frequency of 10 cycles/second (or 10 hertz), and as 10 complete cycles occur in 1 second, the time taken for each cycle is 1/10 of a second (i.e., period).

- **The velocity of a wave;** Velocity = Frequency \times Wavelength

The Frequency Spectrum

When adding sine waves with different frequencies and amplitudes as well as different phase relationships, the resultant waveform is no longer a sine wave but a complex wave pattern. This result is obtained simply by adding the amplitudes of the component waves at every point along their cycles e.g., an arterial pressure tracing or an electrocardiogram (ECG) (figure 5-125).

Any complex waveform can be produced by selecting and adding together appropriate sine waves.

The mathematical process of analyzing complex wave patterns into a series of simpler sine wave patterns is called **Fourier analysis**. This concept helps in understanding the patterns of biological electrical signals. Analysis of the complex waveforms to their sine wave components shows that:

- wave patterns that have sharp spikes have high-frequency components,
- Whereas • wave patterns that are smooth and rounded have low-frequency components.

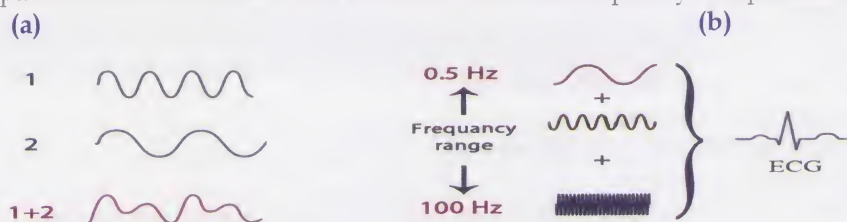


Figure 5-125: Component frequencies of the arterial waveform (a) and ECG (b)

The features discussed in the above part are applied on any wave as electromagnetic, light, and sound waves.

PART 14: ELECTROMAGNETIC WAVES

The spectrum of electromagnetic waves or radiations consists of:

- Gamma rays,
- X-rays,
- Ultraviolet rays,
- Visible light,
- Infra-red rays,
- Microwaves,
- and • Radio-waves.

Electromagnetic waves form part of a continuous spectrum. The spectrum is shown in figure 5-126. It stretches from the very short wavelength and highly energetic cosmic and gamma rays through to the relatively low energy radiowaves.

Only a small segment of wavelengths is capable of stimulating the eye. This is the visible region. The range of this band is from about 390 nm at the ultraviolet rays to 750 nm at the infrared zone.

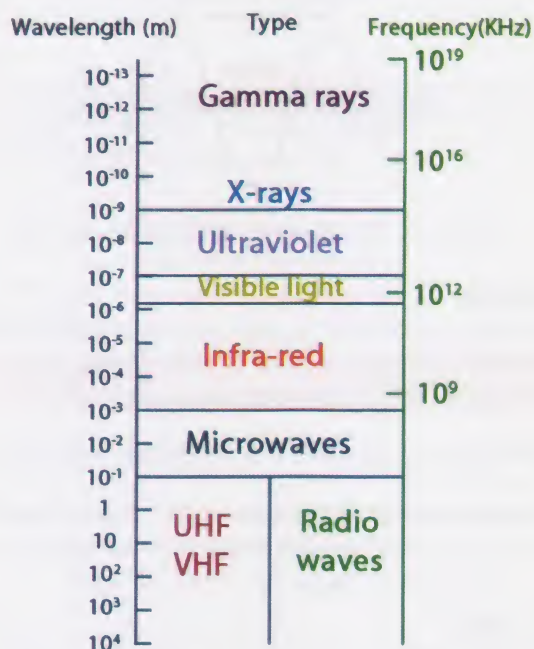


Figure 5-126: The electromagnetic spectrum

Nature and Properties of Electromagnetic Waves

- 1- All propagate electric and magnetic fields.
- 2- All have the same velocity in vacuum. They all travel at the speed of light i.e., 300,000 km/s.
- 3- All are transverse waves i.e., the vibrations occur in planes perpendicular to the direction of the wave.

Features of Electromagnetic Waves:

- Each electromagnetic wave has 3 features:
 - Wave length:** which is the distance between two successive peaks of waves.
 - Frequency:** which is the number of cycles per second.
 - Velocity:** they all have the same velocity.
- Velocity = wave length x frequency.
- Wave length and frequency are inversely related.
- Energy is proportional to frequency.
- Since they all have the same velocity, the distinguishing feature of each electromagnetic wave is either:
 - **The wave length.** It is the most commonly used to define any particular point within the spectrum. The SI unit of the wave length is the nanometer (nm)
 - Millimicron (mμ) and Angström (Å) have been previously used and are now obsolete.
 - $1 \text{ nm} = 10^{-9} \text{ m} = 1 \text{ mμ} = 10 \text{ Å}.$

Or - The frequency. It is the one used in scientific works.

Type of Radiation	Wave length
Gamma rays	Less than 0.01 nm
X-rays	0.01-10 nm
Ultraviolet rays	10-380 nm
Visible light	380-680 nm
Infra-red rays	680 nm-0.1 mm
Microwaves	Few mm- few meters
Radio-waves	Few meters upwards

Clinical Applications:

The region of anesthetic interest in the electromagnetic spectrum that lies within the ultraviolet, visible light and infrared rays.

Ultraviolet rays: are used in ultraviolet halothane meter.

Infrared rays: are used in infrared gas analyzers and infrared spectroscopy.

Visible light: is used in refracto-meter (interferometer), photoelectric cells, photomultipliers, oximeters, spectrophotometers, and colorimeters.

Colorimeters

The original analytical technique of colorimetry was performed by the eye. In the early instruments colors were matched visually in white light against either a selection of permanent colored-glass standards or a series of solutions prepared from known concentrations of the substance under assay. This is a subjective method.

Nowadays, this is replaced with a photoelectric device (made of selenium) that converts the residual or unabsorbed radiation emerging from the sample into an electric current. The magnitude of the electrical signal is related in a defined way to the intensity of the light (figure 5-127).

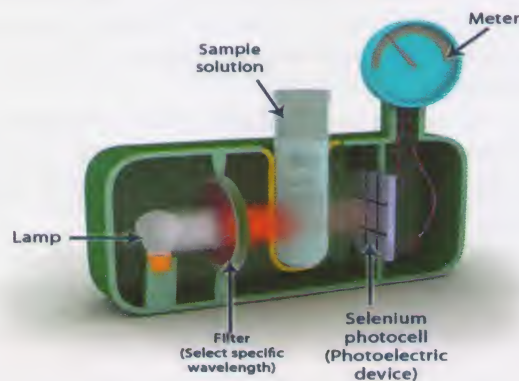


Figure 5-127: A colorimeter

Clinical Applications:

It is used in many laboratory tests e.g., hemoglobin measurement ...etc.

Spectrophotometers

is discussed later.

Clinical Applications:

In many instruments used e.g., pulse oximetry.

Infrared Spectroscopy (Infrared Spectrophotometry)

Many molecules of biological interest absorb wavelengths in the infrared region. The absorptions occurring at infrared wavelengths originate from the natural vibrations of the bonds between atomic nuclei. The bond linking two atoms behaves rather like an elastic force and thus will vibrate in the same way as a spring with a weight at each end.

The stronger the bond is and the lighter the atoms are, the faster the vibration is and the higher the absorption frequency is.

- The source of infrared radiation is a heated nichrome wire. The material under investigation is ground into a fine powder with potassium bromide (KBr). KBr is used:
 - to disperse the radiation.
 - as a supporting medium for studying solid samples.

KBr exhibits very little absorption throughout the infrared region.

The unabsorbed radiation is focused on a thermal detector which detects the change in the temperature.

Clinical Applications:

For example, capnography.

Fluorescence

Idea:

- When energy is applied to a certain molecule, the energy is absorbed and the molecule is excited. After excitation, the electrons in certain molecules instead of returning directly to the ground state pass to a metastable state, intermediate in energy between the ground and excited states. The electrons return from this metastable state to the ground state with the emission of energy in the form of electromagnetic radiation. This process is termed fluorescence.

N.B.: Other molecules when absorb energy, the absorbed energy is dissipated as heat.

Clinical Applications:

For example, fiberoptic O₂ sensor (optode).

Magnetic Resonance Imaging (MRI)

Idea:

Certain atoms produce a **local magnetic field around them**. This magnetic field originates from one of two sites:

a) Nuclear Magnetic Resonance:

- The **nuclei of atoms spin** in their position **in all directions**. These nuclei have electrical charges due to their odd number of protons and/or neutrons i.e., most nuclei **behave like small magnets**. If the protons are in pairs, there will be no magnetic effect because each proton will spin in the opposite direction to the other. This will cancel the magnetic effect.
- This magnetic property possessed by certain atoms **enables** them to **absorb electromagnetic radiation**.
- The magnetic field of the nuclei within the part of the body to be imaged **is placed in the powerful external static magnetic field** of the MRI scanner allowing the **nuclei to align** themselves longitudinally so that they lie parallel to the magnetic field.
 - In the MRI scanner, the nuclei are then turned **out of alignment** with the magnetic field by **applying a short pulse of a second magnetic field perpendicular to the main field**. The nuclei then **process**: they rotate around an axis different from the one around which they were spinning i.e., they **absorb the electromagnetic radiation** which causes the nuclear magnets to be changed from a low to a high energy states. The absorption of this energy can be **measured** from the magnitude of electrical signal induced in a set of coils within the MRI unit. The **detected signals** are then used to **form an image of the body**.
 - After the pulse, which induces nuclear precession, is finished, the nuclei eventually **realign** with the main field and release the energy they absorb. This realignment depends on:
 - The type of the nucleus i.e., the element and its isotope.
 - The molecule in which the element is present; because a molecule produces a small magnetic field which contributes to the total field acting on a particular nucleus, so this can determine presence of the element in different molecules in different tissue types e.g., during studying a hydrogen atom in a particular molecule, the other atoms in the molecule will slightly disturb the natural resonance of the hydrogen atom. Therefore, the hydrogen atom within a methyl group has a different resonance to the same atom in a hydroxyl group, which can give an idea about the type of the tissues.
 - Many isotopes which have this magnetic field can be used e.g.,
 - Hydrogen (¹H or ³H)**: it is the simplest and the most commonly used because:
 - It is abundant in the body as it is one of the constituents of water.
 - It has a strong response to an external magnetic field.
 - Phosphorus (³¹P)**: it is also widely used because of its presence in the molecules of ADP and ATP. This allows different metabolic processes to be studied.

b) Electron Spin Resonance:

The local magnetic field is also produced from the unpaired electrons which spin around the nuclei.

The same behavior occurs on applying an external magnet like the nuclei above.

It is used mainly for studying natural metallo-proteins in the body.

The Magnetic Types in MRI:

Magnets used in MRI units have a magnetic flux density generally between 0.2-4 tesla. This very powerful magnetic field in MRI is created by:

a) **A permanent magnet:** it has the following disadvantages:

- The magnetic field cannot be switched off.
- The magnet is very heavy.

b) **An electromagnet:** it is usually air-cored i.e., without ferromagnetic cores to increase the magnetic flux density. It has the following disadvantages:

- It needs a high coil current
- Much heat is produced due to the electrical resistance of the conductors. Therefore, a superconducting magnet is needed if a higher magnetic field is required.

N.B.: Superconductivity:

The electrical resistance of certain metals and compounds falls to zero when they are cooled to a certain transition temperature. This temperature is different for individual substances but is typically only a few degrees above 0 Kelvin (absolute zero).

For examples, some MRI units use coils made from superconducting magnets. They are made of a superconducting material such as **niobium-titanium alloy**, which is cooled below its transition temperature by immersion in **liquid helium and liquid nitrogen**.

The Room of MRI:

• Magnetic field strength (magnetic flux density) is measured by tesla (T). It is the SI unit. Most scanners use 0.5-1.5 T magnets (one tesla is about 10 000 times the earth's magnetic field). The older unit of flux density is the Gauss (G). One Tesla = 10 000 Gauss.

• The magnetic field decreases as distance from the scanner increases. **5-Gauss line** (which is equivalent to 0.5 mT) is the line that specifies the perimeter around a MR scanner within which the static magnetic field is higher than 5 gauss. Beyond this line or boundary i.e., below 5 gauss (or below 0.5 mT) can be considered safe and the static magnetic field is minimal.

• The actual distance for 5-Gauss line is different in almost every scanner because of differences in actual magnet strength and the type of shielding used by the manufacturer. The actual distance (which can determine the area of the MRI room) can be measured by a manufacturer's service technician.

Clinical Considerations of MRI are discussed in the chapter of "Radiology".

PART 15: LIGHT, OPTICS & LASER

Light is the **visible region** of the electromagnetic spectrum i.e., it is the part of the electromagnetic waves that can stimulate eyes. It has the same features of the electromagnetic waves as:

- wave length (it is in a range of 390-750 nm).
- frequency.
- velocity (it is 300,000 km/s).
- amplitude

Visible or white light consists of all the colors of the rainbow:

Red - Orange - Yellow - Green - Blue - Indigo - Violet.

This fact can be seen when a beam of light passes through a prism. The various colors are refracted by different amounts, and they spread out as they emerge from the prism. The spreading process is called **dispersion** and the color sequence that results is called a **spectrum** (figure 5-128).

Red, green and blue are called primary colors. If such three spots of light are thrown on a screen, the place where they overlap will appear white. All other colors are mixtures of the various spectrum colors.

A red object appears red because it absorbs all colors except red, which is reflected. White objects reflect all colors so they appear white, while black objects absorb all colors, so the black color appears.

Properties of Light:

Light consists of photons. Light has a **dualistic nature** i.e., it can travel as a **wave** or as a **stream of discrete particles** because it has features of both waves and particles.

- **Reflection and refraction** occur with both **particles and waves**.
- **Interference and diffraction** occur only with **waves**.

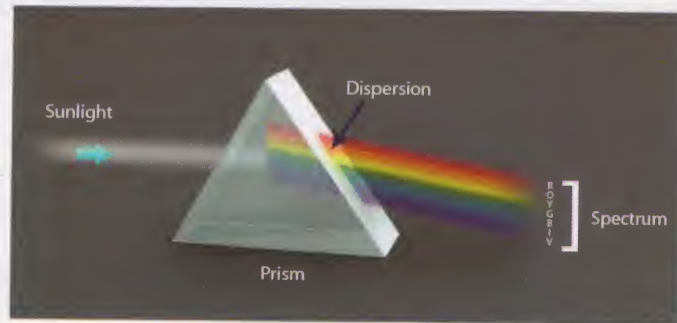


Figure 5-128: light dispersion

Features of Light Waves:

Light waves are **transverse waves** i.e., the vibrations occur in planes perpendicular to the direction of the wave. Light consists of a large number of such waves, each having its own plane of vibration.

1- Reflection: is the turning back of a light wave after hitting a mirror. The angle of incidence is equal to the angle of reflection.

2- Refraction: is the change in the direction of a wave when passing from one medium to the other. The ratio of the sine of the angle of incidence to the sine of the angle of refraction is constant for the two media concerned, and is called the **refractive index** (figure 5-129).

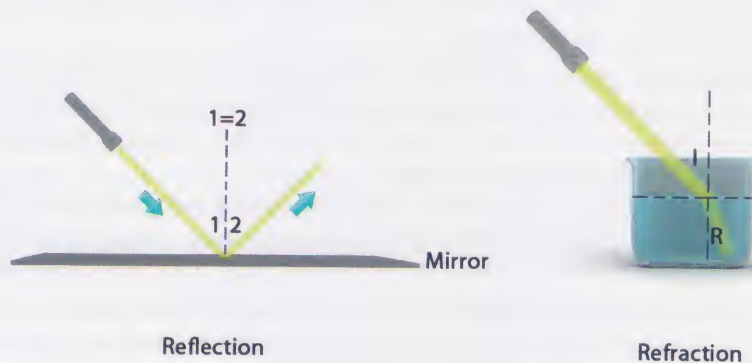


Figure 5-129: Reflection (left) and refraction (right) of light waves

3- Diffraction: is the bending of a light wave when it passes around a corner or through a small opening.

4- Interference: is the net effect of superimposing two sets of light waves. When two waves arrive at the same point, two effects can be produced. If they are in-phase, they reinforce each other. If they are in anti-phase, they cancel each other.

5- Polarization: is the production of vibrations which are parallel to each other in one plane.

Fiberoptics (Optical Fibers)

Idea:

The **direction** in which **light** travels is **bent** when it passes from one substance to another with different optical properties as follows:

- When light passes from a dense medium (glass or plastic) to a less dense medium (air) light is refracted. The angle of refraction is greater than the angle of incidence.
- At a particular angle of incidence, called **the critical angle**, the light is refracted at an angle equal 90° ; therefore, the refracted beam passes along the interface of the two media. Each substance has its critical angle e.g., for glass, it is 42° .
- If the angle of incidence is greater than the critical angle, all the light (i.e., total) is not refracted but reflected into the more dense medium (i.e., internal). This is called **total internal reflection** (figure 5-130).

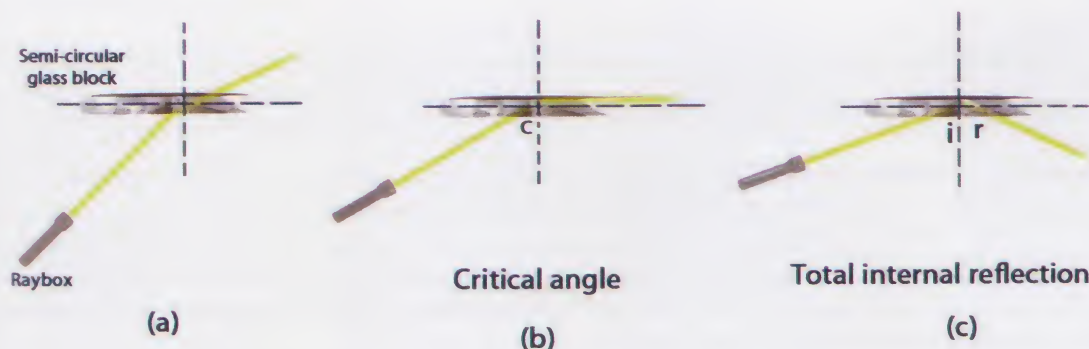


Figure 5-130: Principle of fiber optics

Clinical Applications:

This idea is used in construction of **optical fibers**

An optical fiber consists of a **core** of glass or other transparent material as **plastic** (a dense medium) surrounded by a **cladding or cover layer** (less dense than the core). When light falls on the interface between two materials, it undergoes total internal reflection i.e., **light is continually reflected inside the core** and passes forwards from one point to the next point till it reaches the end of the optical fiber. Each fiber has a diameter of about 20 μm . Many fibers can be grouped to form flexible bundles (figure 5-131). A high-intensity light source is used to provide illumination at the end of the fiberoptics.

N.B.: Light source produces heat also; therefore, it can **burn the patient or cause ignition of the surgical drapes** if it is uncoupled from the endoscope. Therefore, the light source should be switched off before the light guide is disconnected from the endoscope, even if disconnection occurs for a short time.

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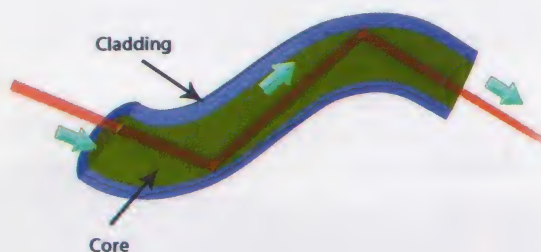


Figure 5-131: An optical fiber.

Uses of Fiberoptics:

1- **Fiberoptic endoscopes:** e.g., laryngoscopes and bronchoscopes.

These instruments contain a bundle of light-conducting fibers which transmit light to the end of the endoscope within a patient's body, and another bundle of image-containing fibers which transmit the image from the lens to the eye-piece of the endoscope.

2- **Fiberoptic monitoring devices:** e.g.,

- Fiberoptic oximetric pulmonary artery catheter for continuous monitoring of pulmonary artery mixed venous oxygen saturation (reflection spectrophotometry).
- Fiberoptic oximetric catheter for continuous monitoring of jugular bulb venous oxygen saturation (reflection spectrophotometry).
- Fiberoptic catheter with a pressure transducer at its tip (Camino) for continuous monitoring of intracranial pressure. The catheter can be introduced into the subdural space, lateral ventricle, or brain tissues.
- Fiberoptic triple fluorescence optode for continuous monitoring of arterial blood gases (PaO_2 , PaCO_2 , and pH). The optode consists of a fiberoptic stand containing specific fluorescent dyes encapsulated at its tip.

3- **Fiberoptic laser:**

The fiberoptic is used to direct the beam of laser from its source to the site where it is needed.

Laser

Definition:

The word "Laser" is an acronym for;
Light Amplification by Stimulated Emission of Radiation

Principles:

- A **high energy (electrical, thermal, or optical)** is applied to the molecules of a laser medium. The laser medium may be gas, liquid or solid. The energy applied is **absorbed by atoms of the laser medium** where the electrons of these atoms can move to higher (excited) energy levels (i.e., an **excited state**). The excited atoms tend to **spontaneously decay** to their original low energy state (i.e. a **ground or normal state**) and in doing so; the energy is often dissipated and **emitted as light or electromagnetic radiations** of specific wavelengths characteristic to each atom.
- The laser medium is present in a tube (similar to a fluorescent light tube) which has windows at each end, **inclined to the path of the radiation at an angle** known as the **Brewster angle**; the angle at which no internal reflection at the surface of the windows takes place. This ensures that 100% of the light is transmitted through the windows.
- In front of each end or window of the tube, there are mirrors between which the radiations are reflected many times. These intense radiations inside the tube cause the atoms to be excited and then return back to the ground state and emit radiations faster than the original one, hence the name **amplification by emission of radiation**. The radiations they emit are exactly in phase with the radiations already passing up and down the tube.
- The result is the conversion of the electrical energy into an intense, narrow, parallel beam of radiation which escapes from the tube through one of the mirrors which is partially silvered (figure 5-132).

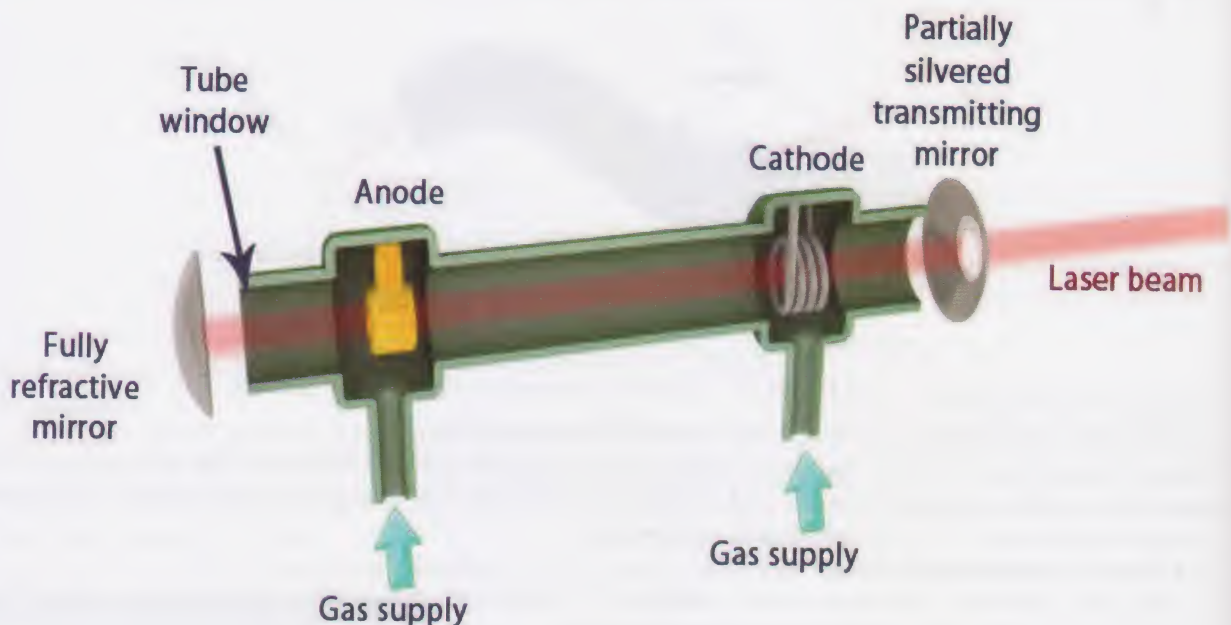


Figure 5-132: A laser device

Features of a Laser Beam: laser light differs from ordinary light in that:

- It is - **Mono-chromatic** i.e., all waves (or photons) possess one wave length.
- **Coherent** i.e., all waves (or photons) oscillate in the same phase.
- **Collimated** i.e., all waves (or photons) exist as a narrow parallel beam.

Types of Medical Laser:

According to its wavelength which is determined by the medium in which the laser beam is generated.

Type	The medium in which the laser is generated	Wave length	Its energy is absorbed by:	Tissue penetration	Uses
1- CO ₂ laser	CO ₂ gas	Long (10600 nm) (invisible, far infrared)	Water and all tissues (it allows shallow thermal effect)	Low	For precise soft tissue surgical cutting and coagulation in almost all types of surgery.
2- Nd: YAG laser	Neodymium-Yttrium-Aluminum-Garnet (solid rod)	Short (1060 nm) (invisible, near infrared)	Darkly pigmented tissues.	Very high (2-6 mm)	For tumor debulking especially in the tracheo-bronchial tree and photocoagulation (gut bleeding).
3- Nd-YAG-KTP laser	Nd-YAG-Potassium titanyl phosphate	Short (532 nm) (visible, emerald green)	Blood (hemoglobin)	Very high	For vascular tumors
4- Argon laser	Argon gas	Short (488 nm) (visible, blue green)	Hemoglobin and melanin	High	For ophthalmic and dermatologic procedures.
5- Krypton laser	Krypton	Short (400-700 nm) (visible, blue red)	Melanin	High	For photocoagulation in ophthalmic procedures.
6- Helium Neon laser	Helium and neon gas	Short 633 (visible, red)			Its red color is used for aiming the CO ₂ and the Nd: YAG lasers.

Effects of Laser on Tissues:

The effect of a particular laser beam on tissues depends on its:

- **Wave length:** generally, the longer the wavelength is, the less the tissue penetration is.
- **Power density:** which is the energy delivered per unit area of cross section (watt/cm²).

Advantages, Hazards of laser, Protective safety measures, and Protocol and management of airway fire are discussed in the chapter of "Otorhinolaryngology".

Interference

Definition:

It is the interaction between two sine waves. The resultant wave depends on the phase of the two wave motions.

Idea:

When two sine waves of the same frequency, amplitude, and phase are added together, the resultant sine wave has a greatly enhanced amplitude.

When two sine waves which are 180° out of phase are added, the resultant sine wave has zero amplitude and appears as a straight line (figure 5-133).

Clinical Applications: It is used in: the refractometer (interferometer); see later "Monitoring of the respiratory system".

N.B.: Interference Filters: They are blocks of material which are transparent to the radiation of interest, but refract the other unwanted radiations.

They are used to select one wavelength from a spectrum of wavelengths.



A

B

Figure 5-133: Addition of sine waves of same frequency and amplitude; having the same phase (a), 180° out of phase (b)

PART 16: SOUND & ULTRASOUND WAVES

The human ear can hear sounds at frequencies within the range 20-20,000 Hz.

In the elderly, the upper limit of audibility is commonly reduced to 15000 Hz or less.

Above 20,000 Hz sound waves cannot be heard by the human ear and are called **ultrasonic waves**.

Nature of Sound Waves

- Sound is caused by vibrations and is a form of kinetic energy. It needs a conducting medium for its propagation and cannot travel through vacuum.
- Sound waves are longitudinal waves produced by a vibrating source and propagated through a conducting medium. The molecules of the conducting medium are compressed and expanded as the wave propagates (figure 5-134).
- The simplest way to visualize wave motion is to consider the action of a plunger which is moved up and down in a regular manner on the surface of water. The plunger interacts with the water particles immediately surrounding it and causes them to oscillate in a similar manner. This oscillatory motion is transmitted in an outward direction from one group of particles to the next and so forms a series of ripples. The maximum displacement of the water surface from its resting level represents the amplitude of the wave, the distance between the crests of the waves represents the wavelength whilst the number of ripples impinging on a stationary object in their path each second indicates the frequency of the oscillation (figure 5-135).

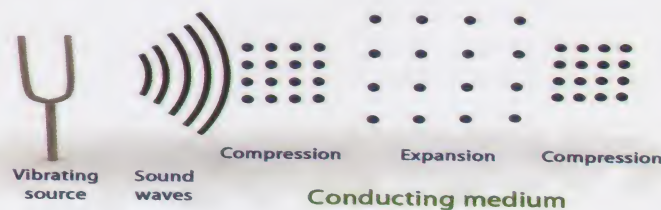


Figure 5-134: Sound waves

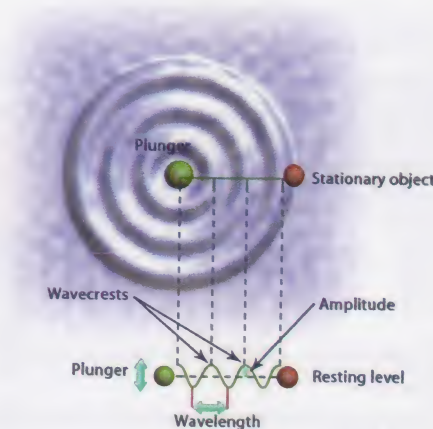


Figure 5-135: Surface view of the plunger creating ripples on the surface of water

Features of Sound Waves

1- Frequency: (hertz)

It is the number of complete cycles per second.

The frequency of the waves determines the **pitch of sound**. The higher the frequency the higher the pitch is and vice versa.

2- Wavelength: (meter)

It is the distance between two successive compressions or expansions, it is the distance between any two corresponding points in two successive cycles, or it is the distance between two peaks or two troughs.

3- Amplitude:

It is the maximum displacement of the wave from the horizontal axis, or in sound waves it is the difference in pressure between the ambient and the peaks of the waveform.

The amplitude of the waves determines the **loudness of sound**. The higher the amplitude, the louder is the sound and vice versa.

N.B.: In light waves, a large amplitude is bright and a small amplitude dim.

N.B.: **The quality of sound** depends on the pattern of the waveform. Sound waves that have regular patterns are perceived as musical sounds, whereas sound waves that have no regular pattern are perceived as noise.

N.B.: **Velocity of the sound:** (meter/second)

Velocity = frequency \times wavelength

Velocity of sound depends on:

- the conducting medium (gas, liquid, or solid)
- and • the temperature

For example, velocity in air is 330 m/s at 0°C,

velocity in air is 340 m/s at 20°C,

velocity in water is 1500 m/s at 20°C,

and velocity in steel is 5000 m/s at 20°C.

Ultrasound Waves

Ultrasound (or ultrasonic) waves are sound waves with frequencies above 20,000 Hz.

In practice, ultrasonic waves of higher frequencies are used, most commonly between 1-10 mega hertz (usually **around 3 mega hertz**).

They are useful in diagnosis. They can penetrate the body without causing ionization.

Generation of Ultrasonic Waves:

Ultrasonic waves are produced by applying an alternating current (AC) to a **piezoelectric crystal (quartz)**. Most of these crystals are made from ceramic materials containing lead zirconate and lead titanate. These substances are very efficient transducers, in transforming mechanical energy to electrical energy and vice versa. These substances act as an emitter and receiver.

a) **An emitter:** on applying a high frequency alternating current (AC) to the two sides of the transducer, its thickness changes and so produces ultrasonic radiation.

b) **A receiver:** when such material is subjected to pressure waves, an electrical current occurs between its surfaces, which can be recorded by wires connected to its surfaces.

Pulsed Ultrasound:

It occurs when the electric current passes to the crystal in the form of pulses. It forms the basis of **pulse-echo technique** used to identify tissue interfaces.

Properties of Ultrasonic Waves:

They include the echo effect and the Doppler effect.

A- The Echo Effect:

Idea:

• Ultrasonic waves are partially absorbed by tissues and partially **reflected** when they hit any surface or at **boundaries** between substances of **different densities** (i.e., **different acoustic impedance**). The reflected waves are called **echo waves**. They are used to form **images** of body structures. This is the basis of sonography (abdominal, obstetric...etc.), echocardiography, and echoencephalography (figure 5-136).

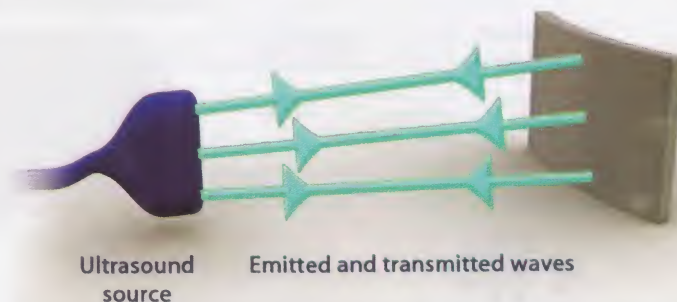


Figure 5-136: The echo effect

- The depth of a boundary or the change in densities can be detected by **measuring the time taken for the ultrasound wave to travel from the transducer and return back** (the transducer is the emitter and receiver). Because the velocity of sound in tissue is relatively constant, the distance is easily measured by the following equation:

$$\text{Distance} = \frac{1}{2} (\text{velocity} \times \text{time})$$

"1/2" because the distance is traversed twice, one to the object and one from it.

Methods of Ultrasound Display (Scanning Techniques)

a- Amplitude Mode or Scan ("A"-Mode or Scan):

- This is the simplest technique. **Pulsed ultrasound** is produced by the crystal (emitter and receiver) which is directed to the area of interest where the probe is coupled to the skin by a liquid coupling medium as oil or water.
- The echoes which are reflected back to the crystal are delayed by **time intervals** that are determined by:
 - the distance of the interface from the transducer,
 - and - the speed of ultrasound in the intervening tissues.

In soft tissues, a time delay of 1 μ s corresponds to a tissue distance of about 1.5 mm (i.e., a tissue thickness of 0.75 mm).

The speed of ultrasound waves in human tissues is about 1540 m/sec.

- The returning signals are **displayed as a spot** which is **then displayed as a vertical deflection (amplitude)** on a sweep of a time base i.e., the received acoustic signals are converted to electric signals with amplitude.

- **Uses** of the A-mode:
 - When the anatomical structures are not complex,
 - when accurate measurement of dimensions is required,
 - and - when differentiation of solids from cystic lesions is required.

For example: - Measurement of fetal dimensions.

- Eye sonography.
- Renal sonography.

b- Brightness Mode or Scan ("B"-Mode or Scan):

- In this mode, the vertical deflection (amplitude) is **displayed as a black/white scale (i.e., brightness)**. Each change in tissue density results in some sound waves being reflected which indicate presence of an interface. This interface is displayed as a line (figure 5-137); for example, in echocardiography, bold lines are seen at the epicardial, the endocardial-chamber, the chamber-endocardial, and the epicardial borders.

c- Motion- or Mono-Mode ("M"-Mode) or Scan :

- In this more advanced mode, **the amplitude bars (brightness) are displayed in a real-time (i.e., time position)**. The echo of this mode is aimed in one direction, so it detects only one dimension of the target structure (the probe or transducer) that does not move.

Uses of the M-mode: It is used frequently in transesophageal echocardiography as it assesses the movement of heart valves and the heart's pumping chambers. It also gives an idea about the size of the heart itself, and the thickness of the heart walls.

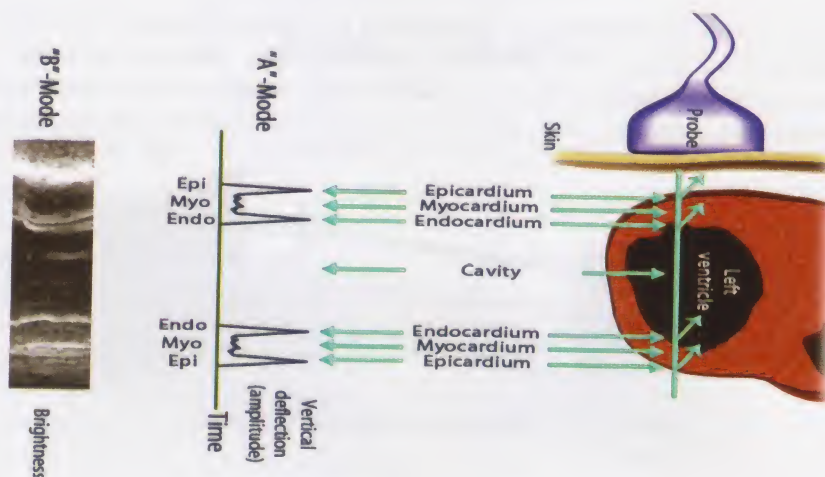


Figure 5-137: A-scan and B-scan

Two-Dimensional Scanning (2-D Echo):

In this scan, the **probe (transducer)** is typically moved across the object (e.g., heart) i.e., the probe is rocked back and forth repetitively. Therefore, the ultrasound beam sweeps in an arc **producing multiple M-mode images** and a panoramic view of the heart is produced which appears cone-shaped on the monitor and cross-sectional images are anatomically recognizable (figure 5-138).

Uses: It is replaced now by the real-time scanning.

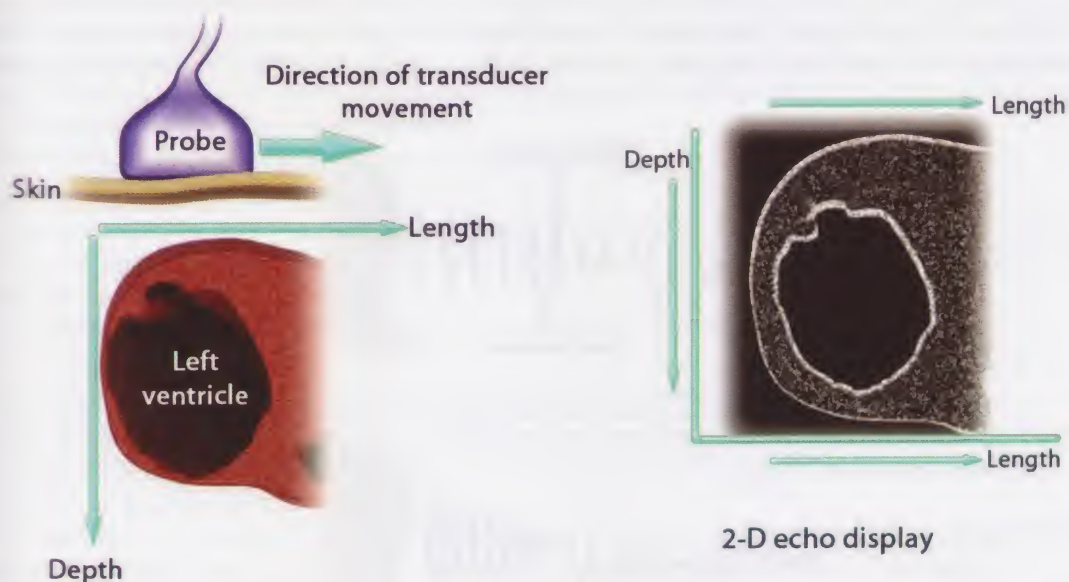


Figure 5-138: Two-D echo

Two-Dimensional Real-Time Scanning:

In **pulsed ultrasound**, the maximum pulse repetition rate is limited by the time taken for the echoes to be emitted, pass through tissues, then to be received by the transducer. **Each pulse can contribute** a single line to the **B-scan**. The rapidity with which an object can be completely scanned will depend on the **number of scan lines** required to build up a **satisfactory image**. Instruments which produce and display images at **more than 20 frames per second** are said to operate in '**real-time**' and **permit moving structures to be studied in great detail**.

There are three types of real-time scanners:

- 1- The probe contains a linear array of about **150 separate transducer** elements arranged in a line. They are **operated sequentially** in small groups to produce a rectangular image of the anatomy lying underneath the probe.
- 2- The probe contains a **transducer which rotates or oscillates to and fro through an arc** by a mechanical motor at a high speed when they contact the skin.
- 3- The probe consists of about **50 transducer** elements mounted in parallel so that they would normally view a field in their long axis.

An operator observes the display and when an image which seems to contain useful diagnostic information appears, the operator stores the image for later study.

N.B.: Ultrasound waves with lower frequency have strong signals, decreased image resolution and penetration, while waves with higher frequency have weak signals, increased image resolution and less tissue penetration.

Clinical applications: It is used in transesophageal echocardiography. It is also used in obstetrics, gynecology, internal medicine, and ophthalmology.

2- The Doppler Effect:

Idea:

Sound waves are regions of high and low pressure in the air, and they travel through it at a fixed velocity. When the source of the sound is stationary, the emitted sound waves will have a particular frequency. When the same source of sound, still emitting the same frequency, starts moving towards the

listener, the high-pressure regions become closer to each other. Consequently, the wavelength of this sound becomes shorter because of the relationship between wavelength and frequency. The ear of the listener picks up this shorter wavelength as an increase in frequency compared with the same source when stationary, and the pitch of the note is higher. Conversely, as a source moves away from the listener, it is heard as a lower pitch because of the decrease in frequency. This is the basis of Doppler Effect (figure 5-139).

N.B.: In 1841, Christian Doppler noted the change in observed frequency from a constant frequency sound generator when the source moved with respect to the observer. Ballot confirmed this Doppler Effect in 1845 with the simple example of the frequency increase in a train's stream whistle as the train approached an observer.

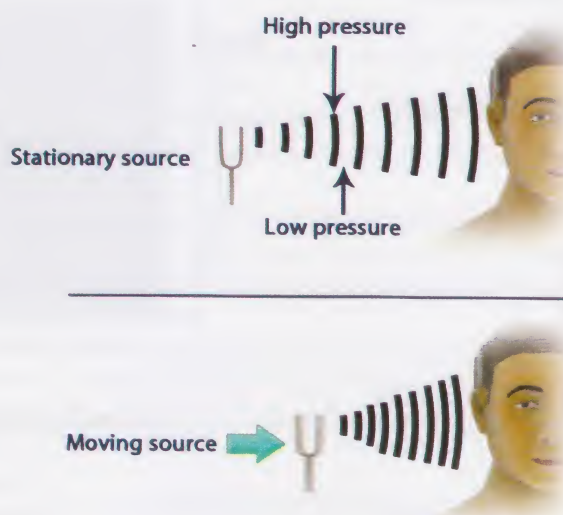


Figure 5-139: Doppler Effect

Therefore,

- When an ultrasound beam is reflected from a stationary object, the frequency of the reflected wave equals that of the transmitted wave. When an ultrasound wave is reflected from an object (e.g., red blood cells in a blood vessel) moving towards the transducer, the reflected wave has a higher frequency (i.e., compressed) than that of the transmitted wave. The reverse occurs when the object moves away from the transducer. The difference between the two frequencies is **a measure of the flow velocity of the moving fluid (blood) and can determine its direction**. This is called **Doppler frequency shift** (figure 5-140) i.e., Doppler effect can measure the velocity and direction of moving red blood cells to and away from the transducer.

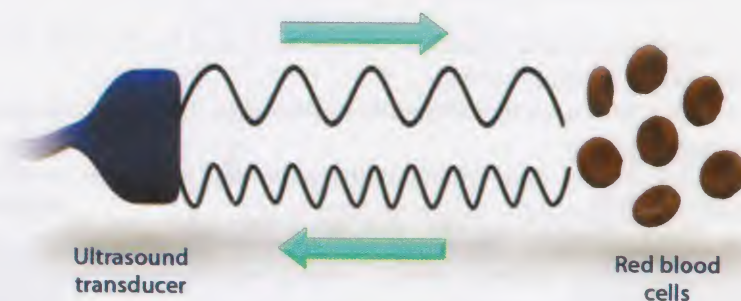


Figure 5-140: Doppler frequency shift

Doppler Effect is either:

a- Continuous Wave Doppler: that is more sensitive.

b- Pulsed Wave Doppler (Range Gated): that is less sensitive. The electricity passes as pulses, and so the ultrasound is emitted and received in the form of pulses. It can receive echo signals from an operator-selectable depth interval (range gated) i.e., the operator can select the depth at which ultrasound waves (and images) are received and obtained.

Duplex Scanners:

• Instruments which **combine 2-dimensional real-time pulse-echo** (to detect the anatomical image) with **Doppler detection** (to detect the velocity and direction) are known as duplex scanners. This instrument allows the sample under study to be positioned precisely in a region of interest identified on the scan, with retaining all the image and Doppler information (velocity and direction of movement) simultaneously.

Doppler Color-Flow Mapping:

• It is a more advanced technology, which combines **2-dimensional real-time pulse-echo** (to detect the anatomical image) and **Doppler effect** (to detect the velocity and direction). The Doppler information, which is related to flow velocity and motion is **displayed on a color map** (i.e., color coded) where

- the **color** indicates the **flow direction**,

and - the **intensity of the color** indicates the **flow velocity**.

This color is superimposed on the anatomical image.

• Determination of a blood velocity allows the **estimation of pressure gradients** as the greater the velocity of blood flow (v), the higher the pressure gradient (ΔP). This is estimated from the modified Bernoulli equation: $\Delta P = 4v^2$

• This allows evaluation of valvular function and intra-cardiac shunting.

Trans-Thoracic and Trans-Esophageal Echocardiography

• Only the component of **blood flow parallel to the Doppler beam** will be analyzed, but blood flow that is perpendicular to the ultrasound beam will not have any Doppler shift and; therefore, will not be presented in the color display.

• For this reason, the probe of ultrasound should be placed in an area (called **ultrasound or acoustic window**) in which the expected blood flow direction is most parallel to the ultrasound.

• In trans-thoracic echocardiography, the probe is held on the chest wall (the chest wall is the acoustic window for the trans-thoracic echocardiography), but during cardiac surgery, the chest wall is in the sterile field and therefore unavailable.

• In trans-esophageal echocardiography, the probe is put inside the esophagus at different areas (i.e., different acoustic windows), away from the sterile chest wall. Also, these different acoustic windows allow more information to be obtained.

Recent Advances and Development in Echocardiography

Echocardiography Probes:

Besides the ordinary **monoplane** and the **bi-plane probes**, there are:

• **Omni-plane probes:** they are now the standard trans-esophageal echocardiography probes. The probe contains a motor in the tip which rotates the transducer through 180 degrees allowing a detailed sweep of any structures of interest.

• **Small pediatric trans-esophageal echocardiography probes:** they allow scan studying of children while they are intubated.

• **Epi-aortic probes:** they can assist in the identification of atheromatous plaques in the ascending aorta and have been shown to reduce the incidence of cerebrovascular injury following cardiac surgery.

• **Intravascular probes:** they are intracardiac catheter-sized probes which can be inserted through the femoral or other large veins allowing visualization of intracardiac structures. It is very useful during closure of atrial septal defects and during catheter ablation of an atrial band for atrial arrhythmias.

Contrast Echocardiography:

Contrast echo can significantly improve definition of the endocardial border and thus significantly improve assessment of the **left ventricular wall contractility**.

Handheld Echocardiography:

Lightweight portable echocardiography is now available which is mainly used for intensive care.

Three-Dimensional Echocardiography (3-D Echo):

Three-dimensional imaging was first developed as an offline reconstruction of 2-D imaging resulting in a three dimensional image of the structure e.g., fetus. Now with the improvement in matrix array transducers, real-time 3-D imaging is produced. It allows understanding the function of the object e.g., mitral valve regurgitation and ventricular geometry.

5- Four-Dimensional Echo (4-D Echo):

It is similar to 3-D echo, but with addition of the time i.e., it gives real-time 3-d imaging for moving objects.

Clinical Applications of Ultrasound Waves:**1- Measurement of blood flow velocity: e.g.,**

- to determine the patency of a peripheral vessel after suspected thromboembolism,
- to determine the patency of an arterial graft.

2- Measurement of blood pressure:

It can sense the onset of systolic flow in indirect blood pressure measurement. The small transducer head is placed over a peripheral artery with the ultrasound beam aligned at an angle of about 45° with the long axis of the artery. As the cuff is deflated, the systolic point is marked by an audible signal corresponding to the intermittent flow through the vessel.

It can also be used to sense the movement of the arterial wall under a sphygmomanometer cuff so that systolic and diastolic points can be established (see later in arterial blood pressure monitoring).

3- Detection of air embolism.**4- Detection of fetal heart sounds.****5- Measurement of cardiac output:**

When combining Doppler Effect with echo effect, the cardiac output can be assessed as the blood flow velocity is assessed by the Doppler Effect, while the cross-sectional area is measured at the arch of the aorta.

N.B.: Uses of Ultrasound as a Physiotherapy Treatment:

When the body is exposed to ultrasound, some of the sound energy is absorbed by the tissues and local heating is produced. The intensity of ultrasound is adjusted to produce local heating without adverse effects on the tissues.

N.B.: Gel:

If an ultrasound transducer is used to emit and receive waves into and out of the body, the waves must pass several times through air, which has a low density, and solid structures, which have a high density. This results in severe attenuation of the signal. Therefore, placing the face of the transducer in a smearing gel on the surface of the skin decreases the differences in the densities and so, reduces the degree of the attenuation of the wave, thereby improving the image.

Further Readings:

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Web Sites:

- <http://www.uwsp.edu/biology/courses/botlab/default.htm>
- <http://www.shodor.org/UNChem/advanced/gas/>
- <http://www.daviddarling.info/encyclopedia/K/kelvin.html>
- <http://mooni.fccj.org/~ethall/gaslaw/gaslaw.htm>
- <http://www.echoincontext.com/doppler01.pdf>
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ANESTHETIC APPARATUS & EQUIPMENT

6

Part 1: Medical gas supplies

- Source of medical gases
- Supply or delivery of medical gases (cylinders and piped system)

Part 2: Pressure reducing valves

Part 3: Flowmeters

- Bobbin Flowmeter "Rotameter®" or Ball Flowmeter
- The emergency oxygen flush valve (oxygen bypass valve)

- O₂ supply failure devices

Part 4: Vaporizers

- Physics of vaporization
- Anesthetic vaporizers
- Modern vaporizers

Part 5: Anesthetic breathing systems (circuits)

- Definition
- Classification: Mapleson system
- The circle system

Part 6: Mechanical ventilators

- Types and classifications
- Monitoring and alarms during mechanical ventilation

- Problems associated with ventilators

Part 7: Scavenging systems

Part 8: Safety features of modern anesthetic machines

- Safety precautions (checklist) of modern anesthetic machines

PART 1: MEDICAL GAS SUPPLIES

An anesthetic machine consists of the following components (figure 6-1):

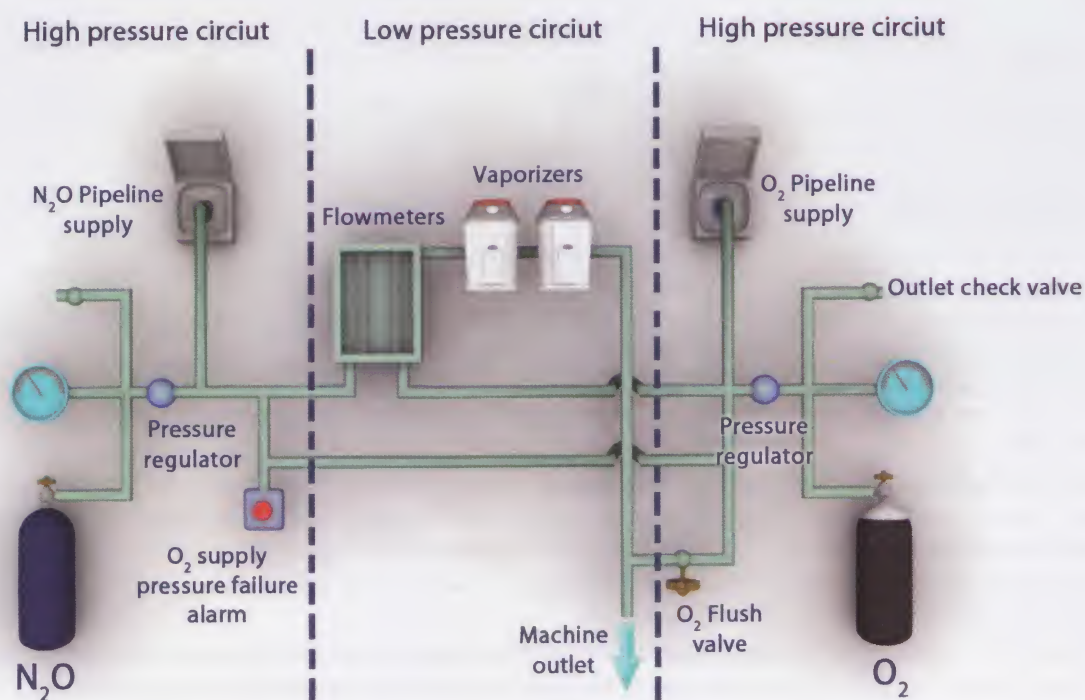


Figure 6-1: Anesthetic machine

1- Supply of medical gases: is either from: - cylinders attached to the machine, or - a central pipeline supply.

They are attached to the machine by appropriate unions.

- 2- **Pressure reducing valves (pressure regulators):** convert the high pressure to low pressure suitable to the anesthetic machine and the patient.
- 3- **A flowmeter:** delivers known flow rates to the vaporizer and anesthetic breathing system and in the same time reduces pressure of gases from 4.1 bar (in the pipelines) to 1 bar, which is delivered to patients.
- 4- **A Vaporizer:** converts the liquid anesthetics to a vapor and delivers known concentrations of the anesthetic vapor to the breathing circuits.
- 5- **A mechanical anesthesia ventilator:** maintains mechanical ventilation to the patient.
- 6- **An anesthetic breathing system (anesthetic breathing circuit):** delivers the anesthetic gases from the anesthetic machine to the patient.
- 7- **A humidifier:** humidifies inspired gases.
- 8- **Monitoring devices:** for the patient and equipment.
- 9- **Alarm systems:** warn against fault or failure of equipment.
- 10- **A scavenging system:** removes the waste anesthetic gases to out side the operation room to minimize environmental pollution.

N.B.: Anesthesia delivery system consists of the anesthetic machine, vaporizer, ventilator, and scavenging system.

Medical Gas Supplies

The anesthesiologists must understand both the sources of the medical gases and the means of their delivery to the operating room to prevent and detect medical gas depletion or supply line misconnection.

Sources of Medical Gases

There are many medical gases that are commonly used in the operating room (oxygen, nitrous oxide, carbon dioxide, air, helium, entonox, and nitrogen).

Medical Gas	Source (Manufactured by)
1- Oxygen (O ₂)	<ul style="list-style-type: none"> • Fractional distillation of liquid air. It produces medical oxygen (99% or 99.5% pure). It is stored in either large insulated containers or cylinders. • Oxygen concentrator. It produces less pure oxygen (90% - 95% pure).
2- Nitrous Oxide (N ₂ O)	<ul style="list-style-type: none"> • Heating ammonium nitrate (thermal decomposition). It is stored in cylinders connected to a manifold.
3- Air	<ul style="list-style-type: none"> • Blending oxygen and nitrogen. It produces medical air. It is stored in cylinders connected to a manifold.. • Compression pumps (central compressor plants).
4- Carbon dioxide (CO ₂)	<ul style="list-style-type: none"> • Heating calcium carbonate and magnesium. It is stored in cylinders.
5- Helium (He)	<ul style="list-style-type: none"> • A natural gas. It is stored in cylinders.
6- Entonox (in UK)	<ul style="list-style-type: none"> • Bubbling gaseous O₂ in liquid N₂O (poynting effect). It is stored in cylinders connected to a manifold..
7- Nitrogen	<ul style="list-style-type: none"> • Fractional distillation of liquid air. It is stored in cylinders.

N.B.: Nitrogen is not given to patients but used to provide power to some operating room equipment such as saws and drills.

Liquefaction of Medical Gases:

Any gas can be liquefied by pressure if its temperature is below a critical level. This temperature is the **critical temperature of the gas**. Above its critical temperature, a gas cannot be liquefied whatever pressure is applied. Cooling and application of pressure both are essential for liquefaction of gases (see before in gas laws).

Critical temperature: is the temperature above which a gas cannot be liquefied by pressure.

Critical pressure: is the pressure required to liquefy a gas below its critical temperature, or it is the vapor pressure of a substance at its critical temperature.

Gas	Critical Temperature	Critical Pressure
Oxygen	- 119°C	50 bar
Nitrous oxide	36.5°C	72 bar
Carbon dioxide	31°C	73 bar
Air	- 140.6°C	

Liquefied Nitrous Oxide:

Because the critical temperature of nitrous oxide (36.5°C) is above room temperature, it can be kept liquefied by application of critical pressure (72 bar), without a cooling or refrigeration system.

N_2O is stored in cylinders, see later.

Liquefied Carbon Dioxide:

Because the critical temperature of carbon dioxide (31°C) is above room temperature, it can be kept liquefied by application of critical pressure (73 bar), without a cooling or refrigeration system.

CO_2 is stored in cylinders, see later.

Liquefied Oxygen:

• Oxygen can be liquefied by pressure below its critical temperature (-119°C). It is **stored at a temperature of -160°C in a special giant vacuum-insulated container** to maintain it at this very low temperature. No refrigeration system is needed for the storage container because the liquid oxygen remains cold due to the efficiency of the vacuum container and loss of latent heat when oxygen vaporizes.

• Gaseous oxygen withdrawn from the top of the container is very cold, so it should be heated to ambient temperature by a **super-heater coil**, then passed through a **pressure regulator** to reduce its pipeline pressure to **4.1 bar** (figure 6-2).

• The **pressure inside the liquid oxygen container is 7 bar**, which is the vapor pressure (VP) of oxygen at -160°C .

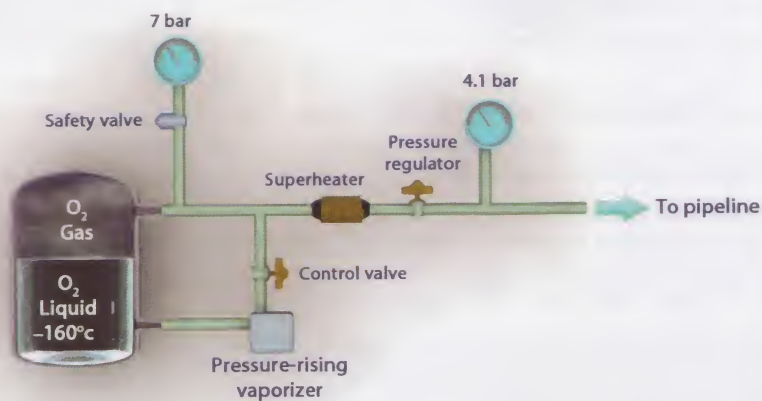


Figure 6-2: Liquid oxygen system

• If the oxygen, from the containers, flows at a fast rate, the temperature of the liquid oxygen falls due to the removal of latent heat, and the **vapor pressure of oxygen falls below 7 bar**. To provide a source of heat to this system, a **pressure raising vaporizer** is used. There is also a **control valve** which senses the pressure in the vacuum-insulated container. When the vapor pressure is decreased below 7 bar, the control valve allows liquid oxygen to be withdrawn from the bottom of the container to the vaporizer to be warmed and vaporized and then returned back to the top of the container and pipeline system to maintain vapor pressure around 7 bar.

• If no oxygen is used, the temperature of the storage container gradually rises until after 1 week the oxygen vapor pressure increases above 17 bar. Therefore, the excess gaseous oxygen is allowed to escape as a waste through a **safety valve** at the top of the container to maintain the vapor pressure around 7 bar.

• The container rests on a **weight balance** to measure the mass of liquid oxygen in the container which is refilled by the gas supplier as needed.

• Even when a hospital has a liquid oxygen plant, it is still necessary to hold **reserve banks of oxygen cylinders** in case of supply failure.

• Liquid oxygen containers should be **kept away from the main hospital building** in an open, cool, well-ventilated area and protected from any heat or ignition source to prevent fire hazard.

• Liquid oxygen is available in some **large hospitals** because it is more economical than oxygen gas cylinders.

N.B.: O_2 is stored in either:

- A special giant vacuum-insulated container as a liquid at very low temperature,
- or • A cylinder as a compressed gas at room temperature, see later.

Oxygen Concentrators

It is a device which concentrates and extracts oxygen from atmospheric air.

Idea:

Atmospheric air is filtered, compressed, and then cooled before being dried by silica gel. Then air passes through two cylinders containing **zeolite (hydrous silicate)** which has ion-exchange properties and acts as a molecular sieve or trapper, separating the oxygen from nitrogen and water vapor in the air and leaving oxygen and other trace inert gases. The nitrogen and water vapor are drawn off by a vacuum pump as waste gas while Oxygen and other inert gases pass to a reservoir then to the patients (figure 6-3).

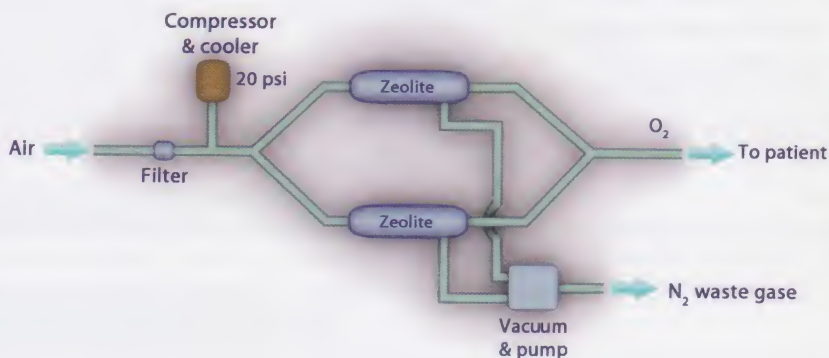


Figure 6-3: Oxygen concentrator

Advantages:

- They produce oxygen concentrations of 90-95% which is suitable for medical uses. There are also small concentrations of nitrogen and inert gases (especially argon) which have no toxic effect.
- Small oxygen concentrators, which can give a maximum flow of 4 liters/min and pressure of 70 kPa, are available and suitable for use in homes for long term domiciliary oxygen therapy (i.e., for domestic use). They are more convenient than oxygen cylinders. The running cost, which includes electricity and servicing, is much less than that of oxygen cylinders.
- Large oxygen concentrators, which can give higher flow and pressures up to 410kPa, are used to operate ventilators and venturis in small hospitals and military hospitals in remote areas and in developing countries.

Disadvantages:

- Larger oxygen concentrators are needed if higher pressure and flows are needed in hospitals.
- They need regular maintenance.
- They should be protected from fire hazards.

Compressed Air Supplies (central compressor plants)

They are more economical for larger hospitals than air cylinders.

Idea:

- Apart from the reservoir, the main units are duplicated so that any item can be serviced or repaired without interrupting the air supply.
- The **air intake unit** is placed out-of-doors where it is not affected by rain, snow, dust or fumes. The air from the intake unit then passes through a **preliminary filter** and a **silencer** then to a **compressor** which incorporates a **cooler** to cool the compressed air. Then the air passes through a **non-return valve** into a **large cylindrical reservoir**.
- After leaving the reservoir, the air is cleaned by **separators and filters** to remove **oil mist** as most compressors are oil-lubricated, otherwise oil pneumonitis occurs.
- The air is then dried by a **silica gel drier** to avoid the increased humidity which increases when the air is compressed.
- The air is then passed through a **final bacterial filter** to ensure that air is free of bacteria (figure 6-4).

Advantages:

The pressure of the air in the pipeline is either: **7 bar**, it is used for operation of surgical tools.

4 bar, it is used for anesthetic machines.

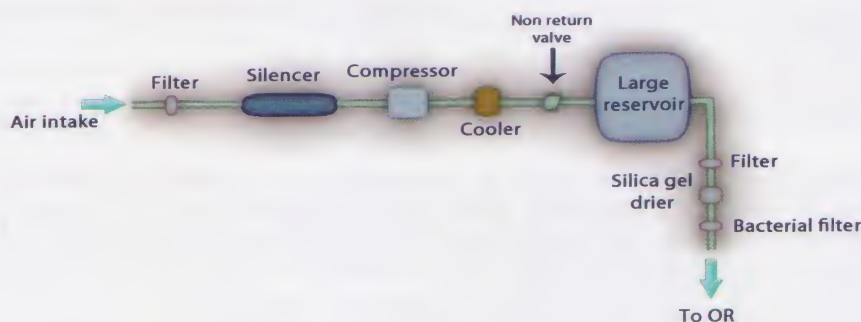


Figure 6-4: Compressed air supply

Supply or Delivery of Medical Gases

The anesthesia machine has 2 medical gas supply sources: - cylinder supply source, and - pipeline supply source.

In some hospitals e.g., military hospitals, oxygen is also derived from oxygen concentrators.

A) Medical Gas Cylinders

Synthesis: Medical gas cylinders are made of a strong metal alloy as **molybdenum steel**, **high carbon steel**, or **manganese steel**. There are cylinders made of **aluminum** (non-ferromagnetic) which are suitable for magnetic resonance imaging (MRI) rooms.

Tests: Medical gas cylinders should be tested by the manufacturer at regular intervals (usually every 5 years) for the presence of defects to ensure that cylinders can withstand higher pressures (about 65-70%) greater than those they are subjected to in normal use. One cylinder in every 100 is cut into strips to test the metal for tensile strength, flattening impact, bend tests, and even internal examinations with an endoscope are performed. The tests are marked by a mark stamped on the neck of the cylinders.

Color: Medical gas cylinders have a color code system specific for each gas. This color code is different in each country.

Gas	Color Code				Form	Pressure at 15°C		Capacities (L)	
	UK		USA	International system		Lb/in (psi)	bar	E-Cylinders	H-Cylinders
	Shoulder	body							
O ₂	White	Black	Green	White	Gas	2000	137	625-700	6000-8000
N ₂ O	Blue	Blue	Blue	Blue	Liquid	735-750	50	1600-1800	16,000
CO ₂	Grey	Grey	Grey	Grey	Liquid	735-750	50	1600-1800	
Cyclopropane	Orange	Orange	Orange	Orange	Liquid	73	5		
Enflonox	White/blue quarters	Blue			Gas	2000	137		6000-8000
Selsum	Brown	Brown	Brown	Brown	Gas	2000	137		
Seliox (21% N ₂ O and 79% Selsum)	White/ brown quarters	Black	Brown/ yellow	Brown/ white	Gas	2000	137	600	
N ₂	Black	Black	Black	Black	Gas	2000	137	625-700	6000-8000
Air	Black/white quarters	Grey	Yellow	Black/white	Gas	2000	137	625-700	6000-8000

N.B.: If an O₂ cylinder is full, its pressure gauge reads 2000 psi (137 bar) and if O₂ flow rate is 3 L/min, the cylinder will be exhausted within 220 min at atmospheric pressure and a temperature of 20°C.

N.B.: 1 bar = 14.7 psi (pounds per square inch).

Size: The size of the cylinders is classified according to their **height** in an alphabetical letter code starting with the letter "A" being the smallest (10 inches height) up to the letter "H" (57 inches height) being the largest;

- Size "E" (31 inches height) is used in anesthesia machines, for patient's transport and for resuscitation.
- Size "H" is the largest and connected by a manifold to form a bank for the pipeline systems.

Capacity: The capacity of the cylinders differs according to the size of the cylinder and the type of the gas or liquid inside them.

Filling Ratio of Cylinders:

As above, the cylinders contain either gaseous form or liquid form according to the critical temperature of the gas.

Cylinders of liquefied gases (as N_2O and CO_2) are never filled to the point where they only contain liquid, because any slight increase in temperature will cause a dangerous rise in cylinder pressure because temperature will cause N_2O or CO_2 liquid to expand, as liquid is not as compressible as gases. The degree of filling of cylinders is expressed by the filling ratio;

$$\frac{\text{weight of substance in cylinder (gas+liquid)}}{\text{weight of water required to fill the cylinder}} \text{ i.e., } \frac{\text{Mass}}{\text{Volume}}$$

The filling ratio of N_2O or CO_2 cylinder is 75% in temperate climate and 65% in tropical climates.

Connections:

Cylinders are attached either:

- Directly to the anesthetic machine especially E cylinders of O_2 or N_2O which serve as a backup if the pipeline system fails or
- To a manifold.

Types of connections:

1- A Pin Index Safety System (PISS):

This system of connection is present in cylinders from size A to E to prevent incorrect attachment of cylinders to anesthesia machine (figure 6-5).



O_2 : position 2 and 5
 N_2O : position 3 and 5
 Air : position 1 and 5
 CO_2 : position 1 and 6
 Cyclopropane : position 3 and 6
 Entonox : position 7



Figure 6-5: Pin index safety system

Each gas cylinder has two holes in the cylinder valve, which mate with two corresponding pins in the yoke (connecting structure) of the anesthesia machine. A flush connection is only achieved if the holes and pins fit correctly. The relative positioning of the pins and holes is unique for each gas.

This design makes it impossible to attach an oxygen cylinder to any yoke other than that designed for oxygen.

2- Direction of the internal thread:

In large cylinders, there is another type of protection. In O_2 , air, helium, and nitrogen cylinders, the internal thread on the cylinder outlet is right handed while in hydrogen and other flammable gases; the internal thread on the cylinder outlet is left handed. This system gives only partial protection against wrong connections (figure 6-6).



Figure 6-6: Internal thread

A pressure Reducing or Regulating Valve:

Is present before the cylinder is connected to the flowmeter of the anesthetic machine, to reduce the pressure from the high pressure inside the cylinder to the low pressure (4 bar) at the anesthetic machine.

N.B.: Cyclopropane cylinders do not require a pressure reducing valve because the pressure inside the cylinder is 5 bar. It is only provided with a fine adjustment valve.

A Bourdon Pressure Gauge:

- Is present to measure the gas pressure inside the cylinder. The pressure in an oxygen cylinder and other gaseous contents is directly proportional to the content of the cylinder, so the pressure gauge can indicate the volume of oxygen (and other gases) remaining in the cylinder. On the other hand, the pressure gauge of the N₂O cylinder will indicate a steady pressure as long as any liquid nitrous oxide remains in the cylinder. When all the liquid is vaporized, the gauge pressure falls steadily until the cylinder becomes empty.

- The pressure gauge of a N₂O cylinder should not exceed 750 psi at 20°C. A higher reading indicates gauge malfunction, liquid overfilling, or faulty presence of a gas other than N₂O.

Latent Heat of Vaporization:

Vaporization of a liquefied gas (e.g., nitrous oxide) and expansion of a compressed gas (e.g., oxygen) require heat, which is extracted from the metal cylinder and the surrounding atmosphere. For this reason, atmospheric water vapor accumulates as a frost on gas cylinders. Heat should be applied locally e.g., by surrounding the valve by a towel soaked in warm water to keep it above the freezing point.

Precautions:

- All gas cylinders are equipped with an **emergency pressure relief valve (rupture disk)** to prevent explosion under conditions of unexpectedly high gas pressure (e.g., unintentional overfilling). The pressure-relief valve is designed to rupture at 3300 psi. The E-cylinder walls can withstand more than 5000 psi, so the pressure-relief valve protects against cylinder explosion.

- Full cylinders are supplied usually with a **plastic dust cover** to prevent contamination by dirt. The cover should be removed just before usage. The cylinder valve should be opened momentarily before attaching the cylinder to the anesthesia machine to blow out any dust which might be lodged in its outlet.

- **Heating cylinders is dangerous** because it increases the pressure inside them. A moderate rise in temperature as occurs in summer, however, is not important because the cylinders are made to withstand pressures well above their normal working range. The cylinders can usually withstand pressure 65-70% above the working pressure.

- Most large gas cylinders are **stored in the upright position**, while some smaller ones and Entonox cylinders are stored horizontally.

- Cylinders should be **stored indoors, protected from the weather** and should not be subjected to extremes of heat or cold.

Nitrous Oxide Cylinders:

- Below 36.5°C (the critical temperature of nitrous oxide), nitrous oxide cylinders contain both gas (vapor) and liquid at a pressure of 750 psi. This pressure remains steady as long as any liquid nitrous oxide remains in the cylinder. When all the liquid is vaporized, the pressure falls steadily until the cylinder becomes empty and the pressure gauge reads zero. The best way to know the amount of nitrous oxide in the cylinder is to weigh the cylinder. Therefore, the **tare weight (or empty weight)** and also the **gross weight (or the full cylinder weight)** of a cylinder containing a liquefied compressed gas as N₂O are often stamped on the shoulder of the cylinder.

- Characters of N₂O cylinders (see above).

Premixed N₂O/O₂ (Entonox) Cylinders:

- Entonox is the trade name for a premixed gaseous mixture of 50% N₂O and 50% O₂. It is prepared by bubbling O₂ gas in liquid N₂O (Poynting Effect).

- When the temperature is above the **pseudo-critical temperature (-7°C)**, Entonox mixture remains in the gaseous state.

Below -7°C, the mixture **separates** into O₂ and some N₂O gas (above) and 80% N₂O and 20% O₂ liquid (below) (due to liquefaction of N₂O). This is a very dangerous situation, because O₂ is drawn off first and the gas mixture at first has a high % of O₂, then the gas mixture becomes progressively anoxic, until at last pure N₂O is drawn off and inhaled by the patient.

To prevent this hazard:

- The cylinders should be **warmed above 10°C**.
- The small cooled cylinders should be **inverted repeatedly before use** to reconstitute the gaseous mixture.
- Large cylinders have a **dip tube** which draws off any liquid phase first. This prevents the delivered O₂ concentrations from falling below 20% at any time (figure 6-7).

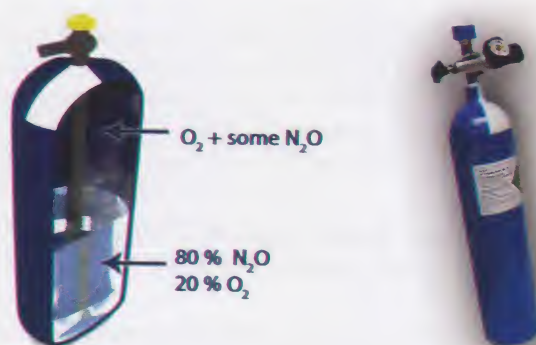


Figure 6-7: Entonox cylinder below -7°C

- The Entonox cylinder has a **special pressure reducing valve** which regulates the output pressure to a **subatmospheric level for self administration** by the patient.
- The Entonox cylinder is widely used in the United Kingdom to produce inhalation analgesia for labor, trauma, dental and minor surgical procedures e.g., removal of chest tubes.
- Entonox is not a single gas but a mixture of two gases; therefore, it is said to have a pseudo-critical temperature rather than a critical temperature.
- Characters of Entonox cylinders (see above).

B) Medical Gas Pipeline System

In many modern hospitals, a central pipeline system for distribution of medical gases has replaced the use of compressed gas cylinders in the operating room (OR), post-anesthetic care units (PACU), and intensive care units (ICU).

Advantages of Pipeline System:

- It decreases the cost.
- It allows more space as there is no need for the presence of large numbers of cylinders in the OR, PACU, or ICU.
- It is more convenient and safe to the personnel and patients.

System Components

It consists of 5 parts:

- 1- Pipeline central supply: includes gas store, valves, and alarm systems.
- 2- Pipeline distribution network.
- 3- Pipeline terminal outlets.
- 4- Flexible color-coded hoses connecting the terminal outlets to the anesthetic machines.
- 5- Connections between flexible hoses and anesthetic machines.

Responsibility for items 1-3 lies on the Engineering and Pharmacy Departments.

Responsibility for items 4 and 5 within the OR, PACU, or ICU lies partly on the anesthesiologists to check the correct functioning of which; therefore, anesthesiologists should be acquainted with the system in the hospital to be able to deal with emergencies that may arise.

1- Pipeline Central Supply:

a) Gas Stores:

Gases as oxygen, nitrous oxide, air, and entonox are stored in **large stored cylinders (size H)** connected together by a **manifold**. A manifold is a tube with several outlets which connect several cylinders of the same type of gas to give a continuous supply. Each manifold system consists of two groups of cylinders on each side. Each group is called a **cylinder bank**. For each gas there are two banks, one in use at one

time and the other as a reserve. The number of cylinders in each bank depends on the anticipated daily demand. When one bank is exhausted, the other reserve bank will work either by a **manual or an automatic (safer) switch** allowing time to replace the empty cylinders in the first bank (figure 6-8).

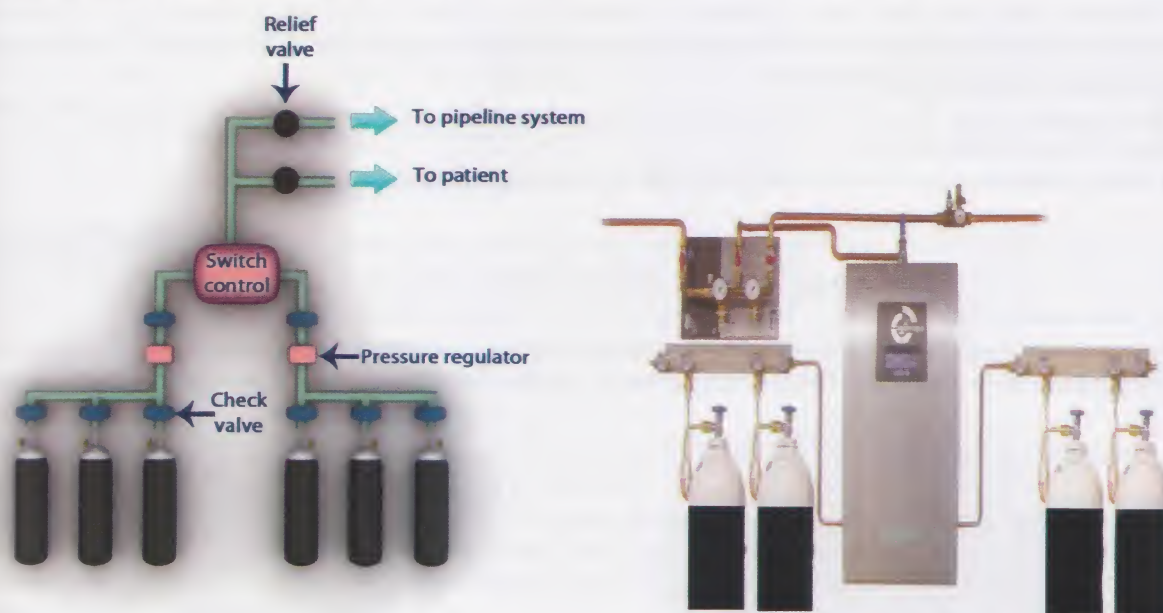


Figure 6-8: A manifold system

Valves:

• Check valve:

This is a non-return or unidirectional valve, which allows gases to pass from the cylinders to the manifold and not the reverse. It is placed between each cylinder lead and the manifold. It prevents loss of gas from the manifold if there is a leak in an individual cylinder or lead.

• Pressure reducing valve (pressure regulator):

This valve reduces the high variable pressure issuing from the gas cylinder banks (e.g., **137 bar** for O₂) to about 10 bar then a 2nd stage reducing valve decreases the pressure from **10 bar** to a low steady and safe working pressure in the pipelines (**4 bar**).

• Pressure relief valve:

This valve is open to the atmosphere to vent excess gases if the pressure in the central pipeline exceeds a preset value. It is usually set at 50% above normal pipeline pressure and closes automatically when the excess pressure has been relieved. This valve protects the anesthetic machines or ventilators from damage by the high pressure.

Alarm Systems (O₂ Failure Safety Devices):

Alarm systems give audible and visual signals if the pipeline pressure increases (e.g., pressure regulator malfunction) or decreases from a preset value which is usually **20-35 psi**. (e.g., supply depletion). The master (central) system monitors the central supply. The area (local) systems monitor each specific area of use i.e., the OR, PACU, and ICU.

1- Pipeline Distribution Network:

- This pipeline network is formed of pipelines which deliver the gases to the site of use e.g., OR, PACU, and ICU.
- Pipes are sized such that the pressure drop across the whole system never exceeds 5 psi.
- Each local line has a manual shut-off and a local alarm system.
- Pipes are made of copper and are color-coded.

2- Pipeline Terminal Outlets:

The pipelines terminate at terminal outlets which are situated usually on the walls, ceilings, or articulating arms at the site of use.

1- Oxygen outlet:

Its color code is **white** and works with pressure **4 bar**.

2- Nitrous oxide outlet: Its color code is **blue** and works with pressure **4 bar**.

- 3- **Compressed air outlet:** Its color code is **black and white** and works with either:
 4 bar for anesthetic machine and ventilators or
 7 bar for instrumental use e.g., orthopedic and neurological instruments.
- 4- **Vacuum outlet:** Its color code is **yellow**. It should be at least 53 kPa (400-500 mm Hg). It is used for surgical suction. Nowadays, it is an integral part of the medical gas system. This system is called **pipel medical gases and vacuum (PMGV)**.
- 5- **Scavenging outlet:** Its color code is **yellow**. It should be **wider in diameter** than other outlets. There is a variety of scavenging outlets.
- 6- **Carbon dioxide outlet:** is present in some theaters for use in laparoscopic surgery.

Connections:

These outlets should have non-interchangeable gas-specified connections to prevent incorrect attachment. This is achieved by a **diameter index safety system (DISS)** which connects the pipeline terminal outlets with the specific flexible hoses. This system varies in design with different manufacturers. The non-interchangeability is achieved by the use of various sizes of collar on the probe so that a given collar only fits the appropriate outlet e.g., the N₂O collar has a larger diameter than the O₂ collar (figure 6-9).

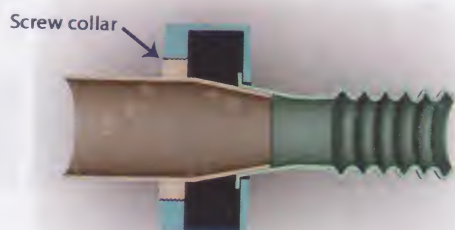


Figure 6-9: Diameter index safety system; many images with different safety systems. Note the difference in connections of oxygen, air, N₂O, and vacuum.

Valves:

Each outlet contains an internal valve which seals the gas supply until the probe is plugged in. On unplugging, the valve closes off the gas supply to prevent leakage of the gas.

4- Flexible Hoses:

They are also color-coded and connect the terminal outlets to the anesthetic machines or ventilators.

5- Terminal Connections:

They are the connections between flexible hoses and anesthetic machines. They are also non-interchangeable gas-specified connections.

Misconnections are fatal especially if the O₂ connections are replaced by another gas e.g., N₂O.

Centralized Vacuum System

Uses: It is used either for: - a surgical suction through a suction apparatus,
 or - a scavenging system.

Components: They are like a compressed air supply. The air passes through the following parts:

- **Drainage traps:** the air from wards and theaters is first drawn into drainage traps to prevent contamination of the system by water.

- **Bacterial filters:** to clean the air.
- **A cylindrical receiver:** The air then passes into a cylindrical receiver which acts as a reservoir to maintain a constant suction. It also prevents the pump, which is on duty, to run continuously when the load is light.
- **Pumps:** Two independent suction pumps should be present. One only works at a time and is capable of maintaining a vacuum of more than 0.67 bar (400-500 mmHg) below the standard atmospheric pressure of 1.01 bar (760 mmHg).
- **A silencer:** The exhaust gases from the pump pass through a silencer before being discharged out-of-doors, usually away from windows or other air intakes e.g., at roof level.

Suction Apparatus

The suction apparatus is connected to the centralized vacuum pipeline system.

Components: (figure 6-10)

- **A collecting jar:** is present between the patient and the suction apparatus to collect the suctioned materials. It contains a **float control** that floats up and closes the jar when it is full, to prevent obstruction of the suction apparatus by the suctioned materials.
- **A filter and another float control:** provide extra protection to the suction unit.
- **A compartment:** in which the vacuum inlet is connected.
- **A pressure control knob and a diaphragm:** The setting of the control knob at the top alters the pressure of the spring on the diaphragm. This in turn varies the pressure at which the diaphragm control valve opens or closes the vacuum inlet, thus adjusting the degree of vacuum.
- **A gauge:** indicates the suction pressure.

Degree of Vacuum:

- Maximum vacuum is usually **more than 0.67 bar (500 mmHg)** which is provided when the pressure control knob is fully opened. This is needed in most general purposes.
- **Lower vacuum** is sometimes needed e.g., during drainage of a closed cavity which is provided by restricting the flow of suction by the pressure control knob.

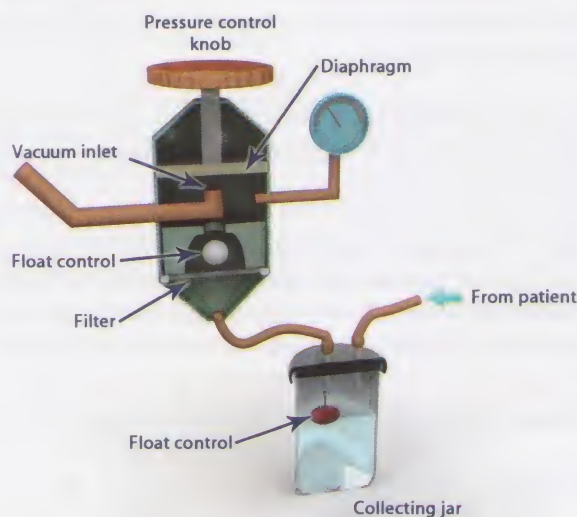


Figure 6-10: Suction apparatus

Safety Features

At Gas Cylinders:

They should have:

- A **color code system** specific for each gas to avoid misconnection.
- A **pressure regulator** to reduce the pressure to **4 bar** to avoid damage of the anesthetic machine.
- A **pressure relief valve (rupture disk)** downstream to the pressure regulators to prevent explosion under conditions of unexpectedly high gas pressure (e.g., unintentional overfilling).
- A special connection system to avoid misconnection and incorrect attachment as a **Pin Index Safety System (PISS)** or a special direction of the internal thread.

- **Filling ratio** i.e., never filled to the point at which they only contain liquid, because any slight increase in temperature will cause a dangerous rise in cylinder pressure.

B) Medical Gas Pipeline Systems:

They should have:

- **A color code system.**
- **A pressure regulator.**
- **A pressure relief valve** which is open to the atmosphere to vent excess gases if the pressure in the central pipeline exceeds a preset value. This valve protects the anesthetic machines or ventilators from damage due to the high pressure.
- A special connection system to avoid misconnection and incorrect attachment as a **diameter index safety system (DISS).**
- **Local and central alarm systems (O₂ failure safety devices).**

Checking out the Medical Gas Supply System in an Operation Room

- Hospitals should have well-defined written policies for management, testing, and control of their medical gas systems and appropriate training of personnel.
- Although anesthesiologists are not responsible for the hospital construction, they are responsible for intraoperative patient safety. In particular, the anesthesiologists are accountable for the portion of the medical gas system that extends from the wall outlet to the patient.
- Checking out the medical gas supply system should be performed in new operation room before the first anesthesia is delivered, and after any maintenance or repairs are carried out on a piped medical gas system.

A) Tests of the Oxygen Cylinders:

Confirm that oxygen cylinders are full (2000 psi) or at least half-full (1000 psi).

B) Tests of the Piped Medical Gas Supply:

Each pipeline should be tested separately.

1- A 24-h Standing Pressure Leak Test:

Medical air is used, where the whole system (each pipeline is tested separately) is pressurized and sealed. Over a period of 24 hours, there must be no drop in pressure.

2- An Anti-Confusion Test:

It is performed by connecting medical air to one pipeline system at a time and ensuring that the test air is delivered from every terminal outlet bearing the name of the gas pipeline system being tested, and not delivered from any other terminal outlet.

3- Purging of the System:

Particulate contamination in pipes may occur, so purging at each affected gas outlet is required to remove loose particles in the pipeline, and to ensure that the pipeline contains only gas from the supply. Purging involves full opening of the valve at each outlet for a period of about 4 min. This test may cause a rapid drop in the gas pressure in the pipeline system which should activate the associated alarms.

4- Checking the Identity and Purity of the Gases Delivered at the Terminal Outlets: by:

- **An oxygen analyzer:** checks the identity by giving readings of 0% for nitrous oxide, 21% for air, 50% for Entonox, and 100% for oxygen.
- **A chemical gas detection tube.**
- Gas chromatography.
- A mass spectrometer.

5- Checking of the Vacuum System:

This is performed by a suction gauge capable of measuring negative pressure.

Common problems include:

- Presence of carbon dioxide impurities; as during pipe jointing procedures, the pipe is filled to a few feet on either side of the joint with carbon dioxide to decrease oxidation while the pipe is heated. Therefore, residual carbon dioxide should be removed by purging.
- Presence of residual copper oxide particles inside the pipeline system.
- Improper joints.
- Inadequate sizing.
- System leaks.
- Components failure e.g., faulty pressure-relief valves.

PART 2: PRESSURE REDUCING VALVES

They are also called **Pressure Regulators**.

Definition

A pressure-reducing valve is a device, which converts a **high variable** pressure from a gas cylinder into a **lower steady** pressure suitable for use in the anesthesia machine i.e., it decreases the values and fluctuations of the pressure.

- The pressure inside a full O₂ cylinder is 2000 psi while in a full N₂O cylinder is 750 psi.
- The reducing valve reduces these pressures to 60 psi (4 bar).

Function (safety features for the modern anesthesia machine)

Production of low steady pressure allows:

- 1- **Easy adjustment** of gas flow rates to anesthesia machines.
- 2- Once the flow is adjusted, **it remains steady**. When the contents of the cylinder are used, the pressure within the cylinder decreases and so, the regulating valve maintains a constant reduced pressure, obviating the need to make continuous readjustments to the flowmeter controls.
- 3- **It prevents equipment damage** by maintaining safe and constant pressure within the machine.

Physical Principle

- Pressure is defined as force per unit area i.e., $P = \frac{F}{A}$

$$\text{So, } F = P \times A$$

- In the simplest form of a pressure reducing valve (figure 6-11), there are two forces (F_1 and F_2) where:

$$F_1 = P_1 \times a \quad \text{and} \quad F_2 = P_2 \times A$$

When there is **no tension in the spring**, balance occurs as the high pressure (P_1) acting on a small area (a) is **balanced** by low pressure (P_2) acting on a large area (A).

$$\text{So, } F_1 = F_2$$

$$\text{Therefore, } P_1 \times a = P_2 \times A$$

Where F_1 = Force on the valve.

F_2 = Force on the diaphragm.

P_1 = High pressure in the cylinder.

P_2 = Low pressure in the reducing valve.

a = Small area of the valve seat of the cylinder.

A = Large area of the diaphragm.

- On **tensing the spring**, a spring force (F_s) is produced which offsets the closing effect on the valve. Thus F_2 may be increased by increasing the force in the spring i.e., $F_2 = F_1 + F_s$

When the low pressure (P_2) falls, the force acting on the diaphragm from below falls and the spring pushes the diaphragm down. When the diaphragm descends, it carries with it a rod connected to a small valve which controls the supply of gas at high pressure (P_1) and so maintains the pressure (P_2) in the compartment below the diaphragm at its correct level (figure 6-11).

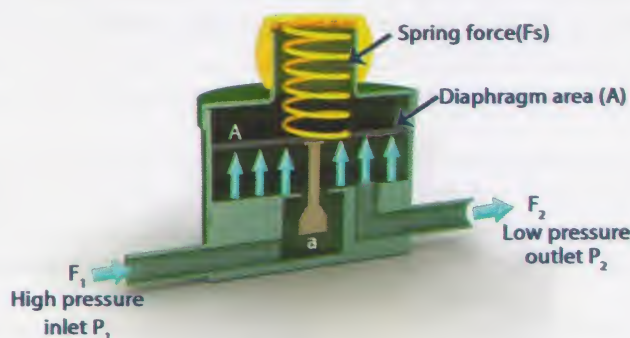


Figure 6-11: Pressure reducing valve (pressure regulating valve)

- Without the spring, the simple pressure regulator has the disadvantage of that reduced pressure decreases proportionally with the decrease in cylinder pressure. The addition of a force by the spring (F_s) considerably reduces, but does not eliminate this problem. In order to overcome this defect, the outflow from the first regulator valve should pass to another pressure regulator valve i.e., a two stage valve.

Types of Reducing Valves

1- Single-Stage Valve:

A single-stage valve consists of one pressure reducing valve. It is suitable for anesthesia machines and oxygen therapy equipment (figure 6-12).



Figure 6-12: A pressure regulator with two gauges; the gauge on the right (nearer to the cylinder, if connected measures the cylinder pressure) while the gauge on the left (nearer to the hoses, if connected measures the output pressure)

2- Two-Stage Valve:

A two-stage valve consists of two reducing valves arranged in series. The output pressure from the first acts as inlet pressure for the second to produce a more steady gas flow.

It is suitable for:

- Laboratory instruments such as gas chromatography, where a steady stream of a carrier gas at a low rate is required.
- Some anesthetic machines have a second-stage valve to reduce O_2 and N_2O from 60 psi (4 bar) to 20 and 38 psi respectively. This is important for proper functioning of O_2/N_2O flow linkage.
- Pneumatic ventilators.

3- Demand Valve:

A demand valve supplies the gas to the patient during inspiration only i.e., when a negative pressure is applied to its outlet.

It is suitable for:

- Entonox cylinders for dental and obstetric analgesia.
- Breathing apparatuses for firemen.

N.B.: Entonox Valves:

- Entonox valve is a special type of two-stage valve used for premixed N_2O/O_2 cylinders.
- It consists of two valves; a single stage valve and a demand valve.
- The flow of gas from the outlet of the cylinder, at first, passes through a first-stage reducing valve. Then the flow passes through a second-stage reducing valve (type of a demand valve).
- The flow of gas from the outlet of the second-stage valve is controlled by a large diaphragm (d). Movements of this diaphragm tilt a rod, which regulates the flow of the gas out of the first-stage valve. The second stage is adjusted so that gas flows only when the pressure is below atmospheric pressure (figure 6-13).

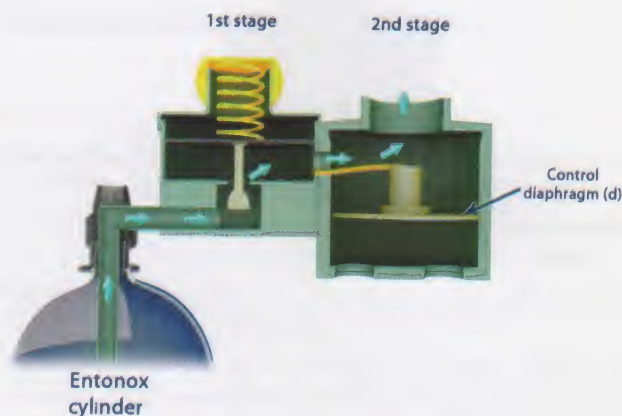


Figure 6-13: Entonox valve

PART 3: FLOWMETERS

Flowmeters on anesthesia machines are classified into:

1- **Variable orifice (constant or fixed pressure drop) flowmeters (Rotameter):** They are the conventional ones used.

2- **Electronic flowmeters:** They are available now in the recent anesthetic machines. In these new machines, there must be a back-up conventional (Thorpe) auxiliary oxygen flowmeter which is used in case of failure of the electronic type.

Other models of anesthesia machines have the conventional flowmeters but measurement of the gas flow is done electronically along the Thorpe tube or there are digital/graphic displays of the flow.

Flowmeters in addition to delivering a controlled flow of oxygen, nitrous oxide, or air, they also reduce the pressure of these gases from 4.1 bar (in the pipelines) to 1 bar, which is delivered to patients.

Bobbin Flowmeter "Rotameter®" or Ball Flowmeter

It is commonly called Rotameter.

Mean: It is the one used in anesthetic machines.

It was invented in Aachen in 1908, first used in anesthesia in 1910, and first placed in an anesthesia machine in 1937.

It is one of the **variable orifice (constant or fixed pressure drop) flowmeters** (see before in flow and volume measurement).

• A **tapered glass or plastic tube** (Thorpe tube), which is narrow at the bottom and wide at the apex like an inverted cone, is present vertically where a light metal alloy **bobbin** (its trade name is Rotameter®) or **ball** is present inside the tube (figure 6-14).

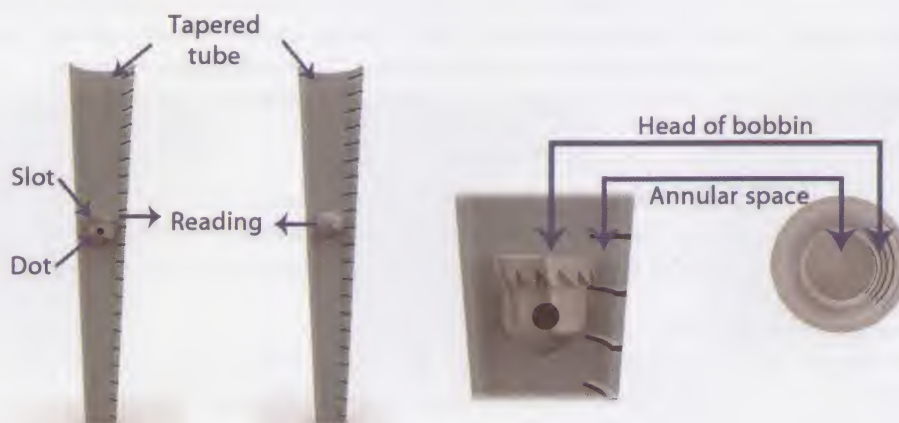


Figure 6-14: Variable orifice flowmeter (Rotameter®)

• When the flow increases, the bobbin or the ball rises in the wider parts of the tube against the gravity and the annular orifice around it increases; therefore, the flow resistance decreases and the clearance around the bobbin or the ball increases. So, the effect of the gravity (weight of the bobbin or the ball) is balanced by the increased flow and so the pressure across the bobbin (or the ball) stays constant although the flow increases.

The reverse occurs when the flow decreases as the bobbin or the ball falls in the narrower parts of the tube and the annular orifice around it decreases; therefore, the flow resistance increases and the clearance around the bobbin or the ball decreases and so the pressure across the bobbin (or the ball) stays constant despite the flow decreases i.e., there is a variable orifice and fixed pressure drop around the bobbin (or the ball).

• At low flow rates, the narrow annular space between the bobbin (or the ball) and the wall mimics a tube and the flow becomes **laminar**. At high flow rates, the width of the annulus is large relative to the height of the bobbin (or the ball), the annular space forms an **orifice** and the flow becomes **turbulent**. Thus at low rates, the **viscosity** of gas determines the position of the bobbin (as it is laminar flow), whereas at higher rates the effect of **density** of the gas becomes more important (as it is turbulent flow).

• At the bottom of the tube, there is a **flow control valve** with a control knob (see below).

Recently electronic flowmeters have been available on the computer screen (figure 6-15).

Factors Affecting the Performance of the Rotameter:

1- The viscosity and density: Because the flow in this flowmeter is a mixture of laminar (at low flow rates) and turbulent (at high flow rates) flow, so both the viscosity (in laminar) and density (in turbulent) of the gas is important. Therefore, each rotameter has to be calibrated for a specific gas i.e., different gases can not be used in the same flowmeter except after recalibration or change of the scale written on the tapered tube.

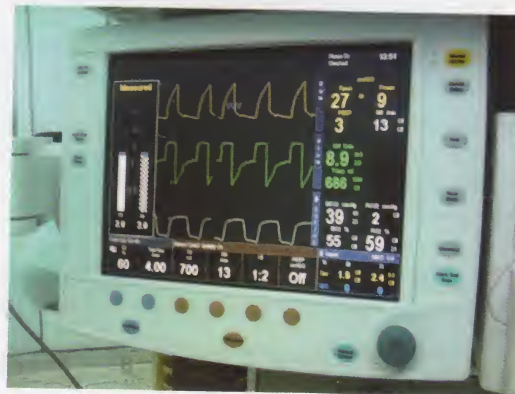


Figure 6-15: Electronic flowmeter on computer screen

2- Sticking: The bobbin may touch the wall of the tapered tube and stick to it. To avoid this:

- The flowmeter tube must be **kept vertical** to reduce the friction between the bobbin and the tube.
- As **electrostatic charges** (which increase sticking) may build up on the bobbin and the wall of the tube if it rubs against the wall of the tube; therefore, to **conduct away the electrostatic charges**:
 - Some tubes are coated from inside by a conductive transparent material (as gold or tin "stannous oxide").
 - A conductive strip is present from inside the tube.
 - The plastic cover of the rotameter is sprayed with an antistatic spray such as Croxtine.
- **Small slots** are placed round the top of the bobbin causing it to rotate centrally in the gas flow and a dot is present in the body of the bobbin indicating its rotation (the dot is not used to indicate the level from which readings are made).
- The **ball** is used as sticking is less.
- **Dust is prevented** by incorporating a **dust filter** in the needle valve at the bottom of the tube because dust on the bobbin may cause sticking or even alteration in size of the annulus which causes inaccuracies.

3- Accuracy: It is within $\pm 2-2.5\%$. To increase the accuracy:

- **Avoid sticking** as above.
- **Readings** are made from the **upper surface** of the bobbin (more accurate as there is a well defined surface for reading) or the central equator (the middle) of the ball (less accurate).
- The caliber of the tapered tube is changed and adjusted with a varying taper (i.e., a **dual taper design**) to allow widening of the scale in the low flow rate i.e., the scale will not be linear. This allows a single flowmeter to read both high and low flows and allows easy adjustment of the bobbin or the ball on the desired flow.
- In recent anesthetic machines where very low flows are needed in closed circuits, **two flowmeters**, one for the low and one for high flows, are made in series and are still controlled by one valve (figure 6-16).
- Attachment of a vaporizer or a ventilator e.g., Manley, after the flowmeter produces back pressure which increases the resistance in front of the flowmeter. This in turn increases the pressure at the outlet of the flowmeter. This increased pressure affects in turn the calibration of the flowmeter, due to affection of the viscosity and density of the gases, which affect the accuracy as there may be as much as 10% more gas flow than that indicated on the flowmeter. Some flowmeters are now pressurized and calibrated to work at a high pressure of several bars, which minimizes the effect of the relatively smaller pressure changes at the outlet.

4- The safety: To increase the safety:

- The **position of the flowmeters** (figure 6-17):

When there are flowmeters in series e.g., one for O_2 and the other for N_2O , and a break in the junction between two flowmeters occurs e.g., in air flowmeter, the concentration of the gas mixture obtained from the flowmeters may be changed and become hypoxic as follows:

If the O_2 flowmeter is located at first and the N_2O flowmeter is located after the air flowmeter, the O_2 may flow out of the break in the system as in (A) and a hypoxic gas mixture is obtained. To solve this problem:

- The sequence of arrangement of the flowmeters is reversed, where the O_2 flowmeter is located after the air flowmeter as in (B). This is the standard in North America.
- Because the standard in most other countries is placement of the O_2 flowmeter at first; therefore, a channel is present at the outlet of the O_2 flowmeter to deliver it separately away from the N_2O (C). This is the standard in the United Kingdom.

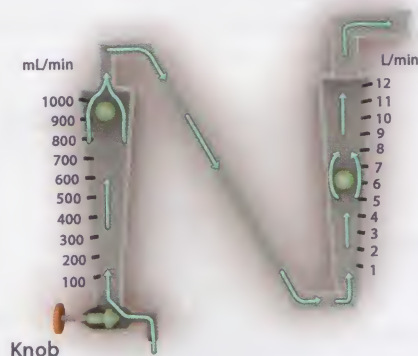


Figure 6-16: Two tube-flowmeter

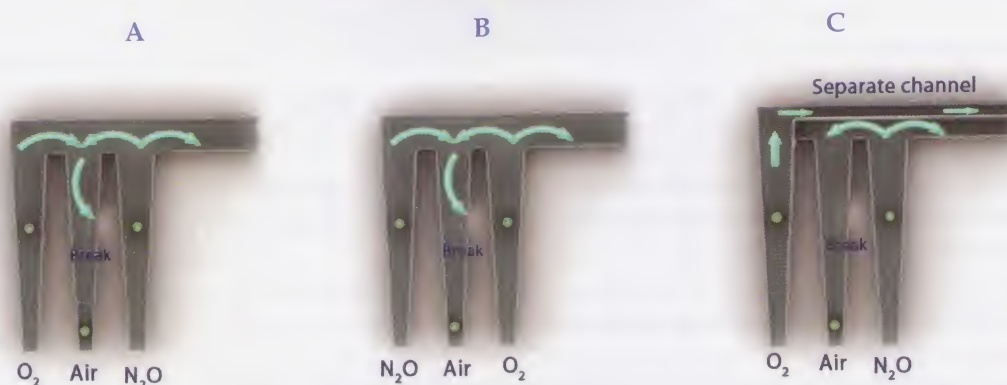


Figure 6-17: Arrangement of the flowmeters

• **Oxygen/nitrous oxide ratio:** In the modern anesthetic machines, there is a link between the oxygen flow controller and nitrous oxide controller to ensure administration of at least 25% O_2 when the N_2O flowmeter is turned on alone. When the N_2O flowmeter is turned on alone, the O_2 flowmeter is turned on obligatorily to at least 25% of the total gas mixture; therefore, hypoxia is avoided. This is achieved by one of the following methods:

3- **A mechanical method:** where a chain link is present between the O_2 and N_2O flowmeter control knobs (Figure 6-18).



Figure 6-18: A chain link between O_2 and N_2O flowmeters

b- A Pneumatic method: where a pneumatic mixing valve is present.

c- An electronic method.

- **Minimum oxygen flow:** Some recent flowmeters allow **minimum oxygen flow** of 150 mL/min O_2 when the anesthesia machine is turned on even when the oxygen flow valve is turned off. This safety feature helps ensure that some oxygen enters the breathing circuit even if the operator forgets to turn on the oxygen flow.

- **The Quantiflex mixer flowmeter** (figure 6-19) eliminates the possibility of reducing the oxygen supply inadvertently because:

- One dial is set to the desired % of oxygen, and it is adjusted first.

- Then the total flow rate is adjusted independently by another dial (the black knob).

Therefore, the percentage of O_2 is fixed and there is no need to readjust the flow of O_2 manually whenever the flow rate is changed.

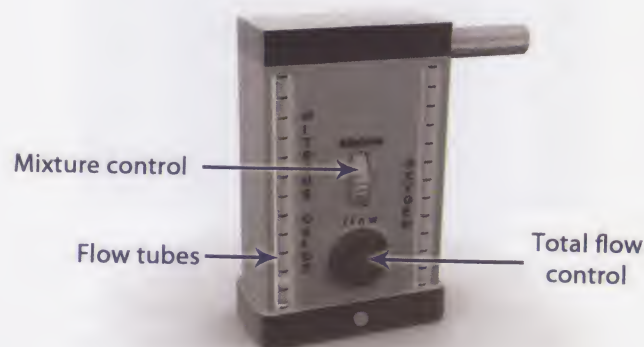


Figure 6-19: A Quantiflex flowmeter

The Flow Control Valves of the Flowmeter:

The valve is a **fine-adjustment needle valve** which controls the gas flow through the Rotameter. When the knob of the flow-control valve is turned counter clock-wise, a needle valve is disengaged from its seat, allowing gas to flow through the valve.

Adjusting the flow control valves of the flowmeter regulates the flow of the gases entering the low-pressure circuit from the high-pressure circuit of the machine.

Safety Features:

- Control knobs have the same color code as the gas cylinders (figure 6-20).



Figure 6-20: Flow control knobs

- The oxygen knob is usually fluted, larger and protrudes further than the other knobs. They constitute an important landmark of the anesthesia machine because they divide the machine into two gas circuits (figure 6-18):

- **The high-pressure circuit:** is the part of the machine that is upstream from the flow control valves and consists of the pipeline system, the gas cylinders and the tubes connecting them to the machine.

- **The low-pressure circuit:** is the part of the machine that is downstream from the flow control valves and consists of the flowmeters, the vaporizers and the common gas outlet that receives all gases and vapors from the machine.

The Emergency Oxygen Flush Valve (Oxygen Bypass Valve)

It provides a high flow (35-55 L/min) of oxygen directly to the common gas outlet at a line pressure of 45-55 psi to provide oxygen in case of emergency as respiratory obstruction.

It is the only device in the anesthesia machine, which directly connects the high-pressure circuit with the common gas outlet bypassing the flowmeters and vaporizers, hence its name.

It is situated downstream from the vaporizer. This leads to:

- Dilution of the anesthetic mixture with excess oxygen, if the emergency oxygen tap is opened partially by mistake and results in the possibility of awareness.
- A much higher fresh gas flow delivered than the anesthesiologist has set on the flowmeter controls.

Due to the high pressure applied, there is a risk of barotrauma of the lung. A protective rim around the flush button may be present to limit the possibility of unintentional activation.

Common (Fresh) Gas Outlet

In contrast to the multiple gas inlets, the anesthesia machine has only one common gas outlet that supplies gas to the breathing circuit. Some new anesthesia machines measure and report common outlet gas flows. An anti-disconnect device (e.g., a screw) is used to prevent accidental detachment of the gas outlet hose that connects the machine to the breathing circuit.

O₂ Supply Failure Devices

These are devices which detect failure of O₂ supply to the anesthesia machine. They include:

1- Alarm Devices:

These are pneumatic or electronic devices activated by oxygen pressure. They give audible and visual signals when the oxygen pressure falls below a certain threshold value.

- In Ohmeda machines, the threshold value is **27 psi**.
- In Dräger machines, the threshold value is **30 ± 3 psi**.

2- Fail-Safe Valves:

These are special valves that sense O₂ pressure in the common inlet pathway via a small "piloting pressure line". They shut off or decrease the supply of nitrous oxide when the O₂ supply fails.

- In Ohmeda machines, the fail-safe valve is known as "**pressure sensor shut off valve**" which is based on a **threshold principle**. The valve is open to nitrous oxide when the oxygen supply pressure is more than 20 psi. When the oxygen supply pressure is less than 20 psi, the valve is shut off to nitrous oxide to avoid hypoxic gas mixture.
- In Dräger machines, the fail-safe valve is known as "**Oxygen failure protection device**" which is based on a **proportional principle**. When the oxygen supply pressure decreases, the pressure of the nitrous oxide will decrease proportionally.

3- Proportional Systems:

They maintain a safe proportional concentration of nitrous oxide and oxygen and in case of oxygen supply failure they maintain a minimal oxygen percentage of 25% and a maximum N₂O: O₂ ratio of 3:1. This is achieved by either increasing the O₂ or limiting N₂O flows.

They are either mechanically or pneumatically based.

- In Ohmeda machines, the system is called "**Ohmeda link-25 proportion limiting control system**" which is **mechanically based**. When oxygen supply fails, it automatically increases the oxygen flow and maintains its concentration at 25% (hence the name link-25).
- In Dräger machines, the system is called "**Oxygen ratio monitor controller**" which is **pneumatically based**. When oxygen supply fails, it automatically limits nitrous oxide flow to maintain an oxygen concentration of at least 25 ± 3%.

Safety Features

1- Flowmeters:

- Methods to **avoid sticking** of the bobbin.
- Methods to **increase the accuracy** as the presence of two flowmeters; one for high flow and the other for low flow.
- **The position of the flowmeters.**
- **Oxygen/nitrous oxide ratio controller** which is either mechanically or pneumatically based.
- **Control knobs** having the same **color code** as the gas cylinders.
- **The oxygen knob** is usually fluted, larger and protrudes further than the other knobs.

2- The Emergency Oxygen Flush Valve (Oxygen Bypass Valve).

3- O₂ Supply Failure Devices.

PART 4: VAPORIZERS

Physics of Vaporization

Definitions:

Vaporization:

- It is the conversion of a liquid to a vapor i.e., in a liquid, molecules are in a state of continuous motion because of mutual attraction by Van der Waal's forces. Some molecules may develop velocities sufficient to escape from these forces, and if they are close to the surface of a liquid, they may escape to the vapor phase.
- It is temperature dependent i.e., increasing the temperature of a liquid increases its kinetic energy (velocities) and a greater number of molecules escapes from the liquid phase and to the gaseous phase forming a vapor.

Latent Heat of Vaporization:

- It is the amount of heat required to convert unit mass of liquid into a vapor without a change in temperature of the liquid.

The faster the moving molecules escape into the vapor phase, the net velocity of the remaining molecules decreases; thus the energy state and therefore temperature of the liquid phase are reduced; therefore extra heat energy is required to keep the temperature of the liquid constant.

- The amount of latent heat of vaporization is affected by the temperature. The lower the temperature is, the more the latent heat is needed. Therefore, the temperature at which the process of vaporization occurs must be specified.

For example, the latent heat of vaporization when 1 kg of water is converted to 1 kg of vapor (steam) is:

2.43 mega J/kg or 583.2 kcal at 20°C i.e., at room temperature

2.42 mega J/kg or 580.8 kcal at 37°C i.e., at body temperature

2.26 mega J/kg or 542.4 kcal at 100°C i.e., at boiling point

- As the temperature increases, the latent heat of vaporization decreases. When the temperature reaches the critical temperature i.e., the temperature at which the substance is completely changed to vapor, the latent heat of vaporization will be zero e.g., the latent heat of vaporization of N₂O is zero at 36.5°C because the critical temperature of N₂O is 36.5°C.

Vapor:

It is the gaseous state of a substance, which exists as a liquid at room temperature and atmospheric pressure. Therefore, - a vapor is the form of substance below its critical temperature,

and - a gas is the form of substance above its critical temperature.

Vapor Pressure (VP):

It is the pressure exerted by the vapor molecules on the walls of the container.

It is temperature dependent.

Saturated Vapor:

In a closed chamber containing liquid and gas, saturated vapor is the vapor which is in equilibrium with its own liquid at a given temperature i.e., when the number of molecules escaping from the liquid is equal to the number of molecules re-entering the liquid phase in a unit time.

Saturated Vapor Pressure (SVP):

It is the pressure exerted by the molecules of the saturated vapor on the walls of the container.

It is temperature dependent i.e., it increases where temperature increases.

It is independent of the ambient pressure.

Saturated Vapor Concentration:

It is the volume percent (vol. %) of a saturated vapor in a gas mixture at a given temperature.

Boiling Point (BP):

It is the temperature at which the saturated vapor pressure of a liquid is equal to the ambient atmospheric pressure.

It is pressure dependent i.e., it is directly related to the atmospheric pressure. Therefore, the boiling point of a given liquid is lower at lower atmospheric pressure e.g., at high altitude.

Vapor Pressure Curve (figure 6-21)

- The curve shows the relationship between: - vapor pressure (on the left Y-axis),
- vapor concentration (on the right Y-axis),
and - temperature (on the X-axis).

- Each anesthetic vapor has its characteristic vapor pressure curve.
- From the curve, three physical properties can be known:
 - SVP (mmHg or kPa) at a given temperature.
 - SVC (vol. %) at any given temperature.
 - BP (°C) at any given pressure.

For example, halothane vapor has the following physical properties at room temperature (20°C) and atmospheric pressure (760 mmHg):

- SVP of halothane = 243 mmHg or 32 kPa at 20°C.
- SVC of halothane = 32% at 20°C.
- BP of halothane = 50.2°C at 760 mmHg.

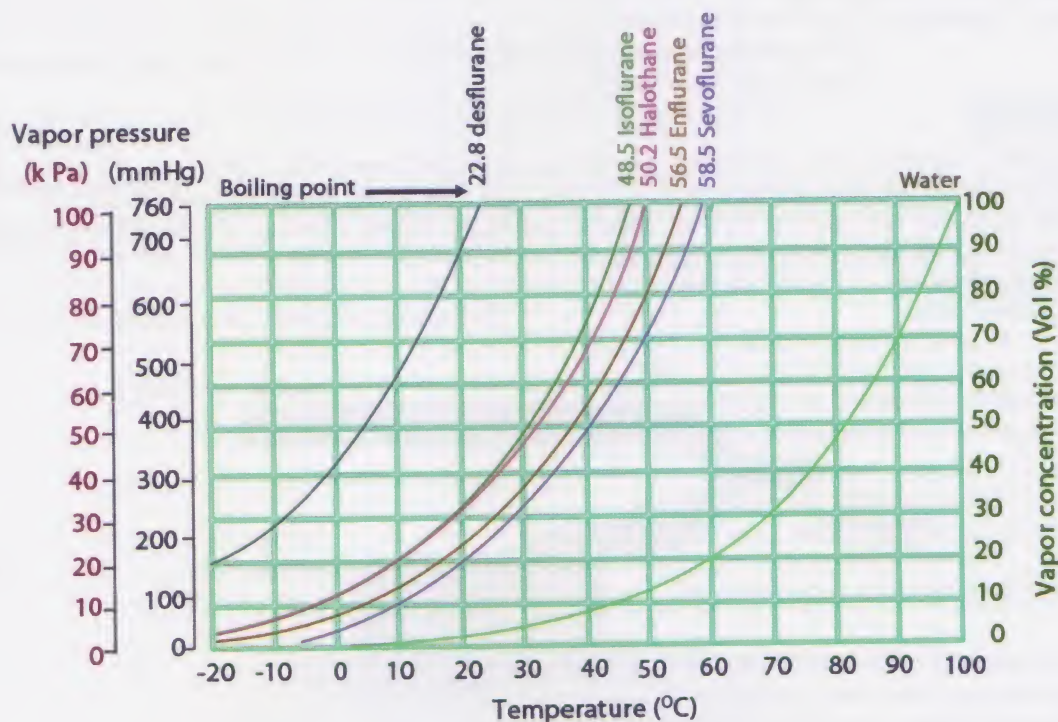


Figure 6-21: Vapor pressure curve

Physical Properties of Common Volatile Anesthetic Agents:

Volatile Agent	SVP at 20°C		SVC (vol. %) at 20°C	BP (°C) at 760 mmHg
	mmHg	kPa		
Halothane	243	32	32	50.2
Enflurane	175	23	23	56.5
Isoflurane	238	32	32	48.5
Desflurane	669	88	88	22.8
Sevoflurane	157	21	21	58.6

N.B.: 1 atmosphere pressure = 1 bar = 100% = 100 kPa = 760 mmHg (1 kPa = 7.6 mmHg).

When the SVP of an anesthetic agent for example, halothane is 32 kPa (243 mmHg) of the atmospheric pressure (100 kPa or 760 mmHg), so its volume concentration is 32% of the total 100%. Always the SVP in kPa is equal in numerical number to the vol.%.

N.B.: Because the SVP of halothane and isoflurane are nearly equal, their physical behavior is nearly the same.

Anesthetic Vaporizers

About vaporizers, the following subjects should be known by the anesthesiologist:

- Definition.
- Classifications.
- Design of vaporizers:
 - Method of vaporization.
 - Cooling effect.
 - Pumping effect.

- Factors affecting the performance of vaporizers:
 - The saturated vapor pressure.
 - The temperature.
 - The splitting ratio.
 - The surface area of the gas-liquid interface.
 - The rate of fresh gas flow.
 - The pumping effect.
 - The position of vaporizers in relation to circle system.
 - The barometric pressure.
- Vaporizer mounting systems.
- Modern Vaporizers:
 - Desflurane vaporizer.
 - The heated-chamber pulsed vaporizer.
 - Aladin cassette vaporizers.

Definition

An anesthetic vaporizer is a device which changes a liquid anesthetic agent into its vapor. It adds a controlled adjusted amount of this vapor to the fresh gas flow (FGF) which has to be delivered. Its use is necessary because the SVP of volatile anesthetic agents at room temperature is several times greater than that required to produce anesthesia.

Classifications

Vaporizers are classified according to:

1- Methods of Regulating Output Concentration:

- Concentration-calibrated or Variable-bypass Vaporizers: used now.
- Measured-flow or Flowmeter-controlled Vaporizers: obsolete.

2- Carrier Gas Flow:

- Flow-over (plenum) vaporizers: used now.
- Draw-over vaporizers: rarely used or obsolete.

Concentration-Calibrated or Variable-Bypass Vaporizers

Idea:

- These vaporizers split the fresh gas flow into two streams (figure 6-22):
 - One stream bypasses the anesthetic gas (and hence the name).
 - The other stream enters the vaporizing chamber to carry anesthetic vapor.

The two streams then reunite and remix at the common outlet of the vaporizer before passing to the patient.

- The ratio of the bypass gas to that entering the vaporizing chamber is called the **splitting ratio**.

$$\text{Splitting ratio} = \frac{\text{Gas flow by passing the vaporizer}}{\text{Gas flow entering the vaporizer}}$$

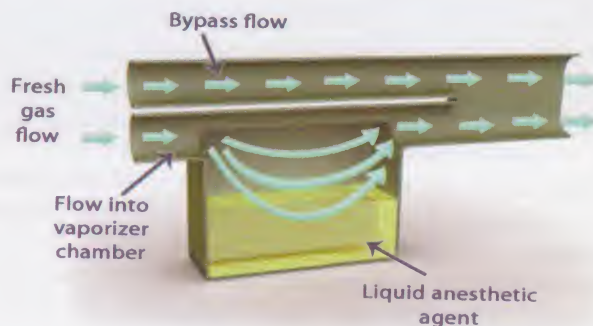


Figure 6-22: Simple type (variable-bypass) vaporizer

- The amount of the flow passing through the bypass channel (the splitting ratio) and the output concentration of the vaporizer are controlled by a **concentration control dial** calibrated in volume percent (and hence the name).

• For example, in an isoflurane (or halothane) vaporizer at a room temperature of 20°C, the SVP of isoflurane at that temperature is 32 kPa. If the ambient atmospheric pressure is 100 kPa i.e., 1 bar, the concentration of vapor in the vaporizing chamber is 32% (an example of Dalton's law of partial pressures). If the control valve is set to allow 5% of the incoming gas to flow through the chamber and 95% through the bypass channel, the resulting concentration of isoflurane is 1.6%. The concentration remains the same provided that the temperature is constant and the surface area of liquid isoflurane within the chamber is large enough to maintain the SVP.

The SVP of an anesthetic agent such as isoflurane is much more in excess than that required to maintain anesthesia. If a fault occurs e.g., in the control valve, an unintentionally high proportion of gas may pass through the vaporizing chamber carrying a risk of overdose and fatality.

Uses: All modern vaporizers e.g. Tec 4, Tec 5, and Vapor 19.n vaporizers.

Measured-Flow or Flowmeter-Controlled Vaporizers

Idea:

• An accurate flowmeter provides a measured flow of oxygen to the vaporizer, all of which passes to the vaporizing chamber where it bubbles through the volatile anesthetics and becomes fully saturated. Because the SVP of the volatile anesthetics is greater than the partial pressure required to anesthetize a patient, the saturated gas is diluted by a known flow of fresh gas through the anesthesia machine to produce the final desired concentration (figure 6-23).

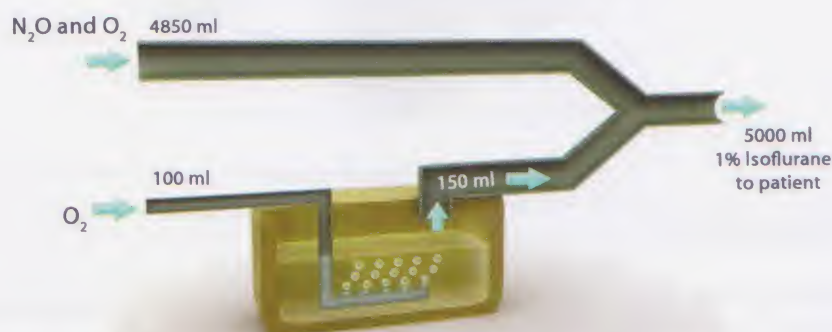


Figure 6-23: A copper kettle vaporizer

• For example, the SVP of halothane is 243 mmHg (32 kPa) at 20°C, so the concentration of halothane exiting a copper kettle at 1 atmosphere (760 mmHg) would be 243/760, or 32%. If 100 mL/min of oxygen enter the vaporizing chamber of the kettle, 50 mL/min of halothane vapor are added and therefore, roughly 150 mL of oxygen and halothane exit from the vaporizing chamber.

In contrast, a partial pressure of only 7 mmHg or less than 1% concentration (7/760) at 1 atmosphere may be required for anesthesia. To deliver a 1% concentration of halothane, 50 mL of halothane vapor and 100 mL of carrier oxygen gas that left the copper kettle have to be diluted with another 4850 mL of gas when the flow is 5 L/min (5000-150 = 4850). When the total flow is fixed, the concentration of an anesthetic agent is determined by changing the flow of the gas entering the vaporizing chamber. If total gas flow falls unexpectedly (e.g. exhaustion of a nitrous oxide cylinder), the dilution of the anesthetic gas decreases, and so volatile anesthetic concentration rises rapidly to potentially dangerous levels.

The same principles are applied to isoflurane.

Uses: Cooper kettle vaporizer. It is now obsolete.

Flow-Over (Plenum) Vaporizers

Idea:

• The gas flow obtained from pipelines or gas cylinders is forced through the vaporizer by the pressure of the fresh gas supply at the back bar of the anesthetic machine. The gases which enter the vaporizing chamber will flow over the liquid anesthetic agent and become saturated with its vapor.

• These vaporizers should have high resistance to gas flow; therefore, they are not suitable for use as draw-over vaporizers.

Uses: All modern vaporizers and the Boyle's bottle.

N.B.: **The Boyle's Bottle** (figure 6-24)

It is of historical interest. It consists of:

- A glass bottle: containing the anesthetic gas.
- A rotary valve: controls the proportion of the gas flowing through the vaporizing chamber and that flowing through the bypass channel.
- A control lever: - When it is in full position i.e., upward, all the fresh gas flows directly over the surface of the anesthetic agent so a high concentration of anesthetic agent is produced as in induction of anesthesia.
- When the control lever is rotated downwards, part of the gas flow is diverted through the bypass channel so, a low concentration of anesthetic agent is produced.
- A plunger and cowl: can direct the gas stream closer to the surface of the liquid or even enable it to be bubbled through the liquid anesthetic agent thus increasing the concentration of the volatile agent.

Because the output of the Boyle's bottle is so variable, it cannot be calibrated.

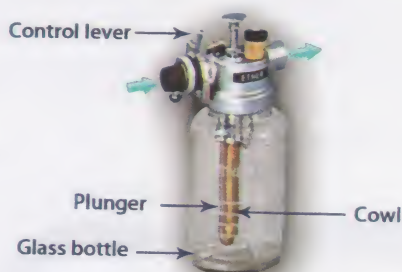


Figure 6-24: The Boyle's bottle

Draw-Over Vaporizers

Idea:

Air or gas as O_2 (N_2O is never used) is drawn over into the vaporizer by the patient's inspiratory effort creating a subatmospheric pressure (see later in "anesthetic breathing systems").

These vaporizers should have low resistance to gas flow to allow easy inhalation by the patient.

Patients are either spontaneously breathing or mechanically ventilated.

Uses: usually in **portable vaporizers** in portable anesthetic machines, they need no cylinder gas supplies, so they are ideal for use outside hospitals for emergency, in major disasters, or in remote areas e.g.,

1- **EMO** (Epstein and Macintosh of Oxford) ether vaporizer (figure 6-25):

It has a bellows thermal compensation device. It is heavier than the other vaporizers. It has a water reservoir to aid thermal stability (see later). It is designed for use with ether (halothane cannot be used).

It works more efficiently when the oxygen is not available and works less efficiently when a continuous flow plenum system is connected to it, as a lower percentage of anesthetic than indicated is produced.

2- **OMV** (Oxford Miniature Vaporizer):

It has a small heat-retaining water reservoir to aid thermal stability but there is no thermal compensation valve. It is designed for use with halothane, trichloroethylene or enflurane.

It works efficiently when a system of oxygen supply is present, either continuous or intermittent flow or even with a draw-over technique (figure 6-26).



Figure 6-25: EMO vaporizer



Figure 6-26: OMV

3- The Triservice Vaporizer:

It is incorporated in the Triservice apparatus which was designed by the British armed forces for use in battle conditions. The Triservice apparatus comprises a self-inflating bag, a non-rebreathing valve (e.g., Ambu E) which vents all expired gasses to the atmosphere, one or two Triservice vaporizers (which have a low internal resistance), an oxygen supply, and a length of corrugated tubing which serves as an oxygen reservoir (figure 6-27).

The Triservice vaporizer is a **modified OMV** where the heat-retaining reservoir contains antifreeze instead of water so that it is not damaged at low temperature and can work even in winter or cold conditions.



Figure 6-27: The Triservice apparatus

4- PAC (Portable Anesthesia Complete) Vaporizer:

It is conveniently compact, so its performance is not affected by shaking, tilting, or transient overturning (an advantage for vaporizers used in the field). It contains bimetallic strip temperature compensation (see later). It can be used in a plenum or draw-over system (figure 6-28).

5- Vaporizers (Inhalers) for methoxyflurane or trichloroethylene, used for **self-administration** by the patient to produce obstetric analgesia (obsolete now).

6- Goldman Draw-Over Vaporizer:

It is used in anesthetic machines where it is incorporated inside the breathing system (figure 6-29).



Figure 6-28: PAC



Figure 6-29: Goldman vaporizer

Design of Vaporizers

Certain aspects have to be considered in the design of vaporizers, these include:

- The method of vaporization.
- The cooling effect.
- The pumping effect.

1- Method of Vaporization:

The efficiency of vaporization can be improved by increasing the surface area of carrier gas-liquid interface. This will produce full saturation of the gas by the volatile anesthetics; therefore, avoiding the effect of flow on the degree of saturation, and so the concentration of volatile agents becomes **flow independent**.

Methods of Increasing the Surface Area:

A) Wicks:

Idea:

Metal or fabric wicks are present in the vaporizing chamber; one end of each is **immersed into the anesthetic liquid**, while the other end projects up into the chamber. The liquid anesthetic moves up the wicks by **capillary action**.

The carrier gas travels through a **concentric helix** which is bounded by the fabric wicks to avoid streaming of gas through the vaporizing chamber and ensure efficient vaporization (figure 6-30).

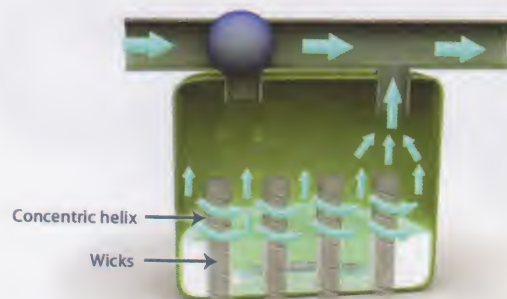


Figure 6-30: Wicks

Advantages of Wicks:

- They provide a large surface area.
- They compensate for drops in the liquid anesthetic level (level compensation) i.e., they maintain the surface area despite gradual emptying of the vaporizer.

Uses: in most modern vaporizers as Tec series of vaporizers.

B) Bubbling:

Idea:

The carrier gas is bubbled through the liquid anesthetic. This is achieved by either:

- Directing the gas through a moving plunger to be immersed in the liquid anesthetic e.g., Boyle's bottle, or
- Allowing the gas to pass through a special diffuser (a sintered disc of glass or metal) at the bottom of the vaporizer to produce tiny bubbles e.g., copper kettle or Halox vaporizer.

2- The Cooling Effect:

Vaporization produces progressive cooling because it needs heat energy, which is supplied by the liquid anesthetic. Thus, the output vapor concentration of the vaporizer decreases with time.

Methods of Decreasing the Cooling Effect:

A) Heat Supply: either by:

- **Thermal Conductivity and Specific Heat:** e.g., copper kettle vaporizer.

The vaporizer is made of a **large mass of copper** (e.g., the weight of copper kettle is about 5 kg) which has:

- **High thermal conductivity** i.e., copper has **high speed of heat conduction** through its substance, so it can supply heat from the atmosphere to the vaporizer (unlike the glass of the Boyle's bottle which is a poor conductor of heat and prevents effective conduction of heat by its surroundings).
- **High specific heat** i.e., copper needs high quantity of heat to raise the temperature of 1 gram of its substance by 1°C. So, the copper itself acts as a **reservoir of heat** to delay and decrease temperature fluctuations, as the heat capacity of the copper is added to that of the anesthetic agent in the vaporizer.

Although the specific heat of copper is not as high as that of the anesthetic agent e.g., as halothane, copper is very dense and the large mass present in a typical vaporizer gives an important contribution to the heat capacity.

- Some vaporizers use **water** as a heat reservoir because it has high specific heat capacity.

- **Electric Heater:** e.g., Tec 6 desflurane vaporizer.

A thermostatically controlled electric heater supplies heat to the vaporizer to maintain it at a constant temperature (39°C).

Thermal Compensation:

These vaporizers have a mechanism which produces an increase in flow through the vaporizing chamber (i.e., an increased splitting ratio) as the temperature of the liquid anesthetic decreases. This is achieved by:

- **A manual mechanism:** in **measured-flow vaporizers** e.g., copper kettle and Halox vaporizers.

The output vapor concentration is adjusted manually by rotating the control dial according to the temperature of the liquid anesthetic as measured by a built-in thermometer.

- **A computerized mechanism:** in **electronic vaporizers**.

The output vapor concentration is adjusted according to the temperature by a computerized control device.

- **An automatic mechanism:** in **concentration-calibrated vaporizers**.

The output vapor concentration is adjusted according to the temperature by an automatic temperature-sensitive device. Three types are available:

- 1- **Bimetallic strip:** e.g., in Tec series vaporizers.

It consists of two different metals (which have a different coefficient of thermal expansion) welded together, so they expand and contract differently in response to temperature changes. This different expansion and contraction will bend the strip which in turn controls a valve. The valve controls the flow through the exit port of the vaporizing chamber. Therefore, when the temperature decreases, the strip bends allowing more gas to pass through the vaporizer (the reverse occurs when the temperature rises).

- 2- **Metal bellows:** e.g., in EMO and Ohio vaporizers.

It consists of a bellows which contains a fluid with a high coefficient of expansion. When the temperature decreases, the bellows shortens and in turn controls the valve (the reverse occurs when the temperature rises).

- 3- **Metal rod:** e.g., Vapor 19.n

It consists of a metal rod which has a high coefficient of expansion. It acts in a similar way (figure 6-31).

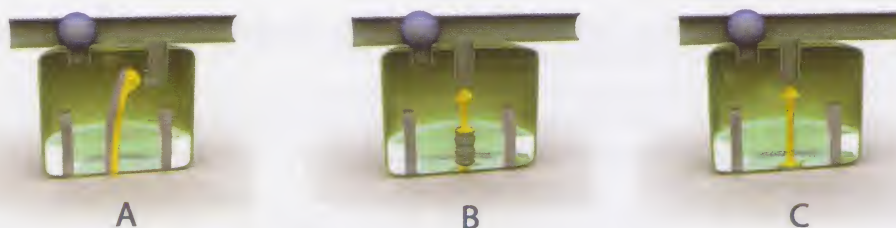


Figure 6-31: Automatic thermal compensation; bimetallic strip (A), metal bellows (B), and metal rod (C)

The Pumping Effect (Intermittent Backpressure effect):

It occurs when the vaporizer is used with intermittent positive pressure ventilation especially:

- with gas-driven mechanical ventilators as Manley.
- at low flow rates.
- at low dial settings
- at low levels of liquid anesthetic in the vaporizing chamber.

During the **inspiratory phase** of mechanical ventilation, there is a **retrograde** transmission of positive pressure from the anesthetic circuit to the vaporizing chamber creating a great **increase in pressure** in the outlet port and back bar of the anesthetic machine. This increased pressure compresses the gas in the vaporizer. **Some gas** in the region of the outlet port of the vaporizer is forced **back into the vaporizing chamber** where more vapor is added to it. Also some gas may pass retrogradely from the vaporizing chamber to the inlet tube to reach the bypass tube (especially when the vaporizing chamber is larger in

volume than the bypass chamber). Therefore, there is a temporary **surge in anesthetic concentration** when pressure decreases at the end of the inspiration. This increased concentration of the anesthetic leaves the vaporizer to the patient.

Methods of Decreasing the Pumping Effect:

- 1- By using a **long spiral inlet tube** to prevent the retrograde vapor from reaching the bypass tube e.g., in vapor 19.1 and Tec mark 3 vaporizers.
- 2- By **decreasing the size of the vaporizing chamber** to decrease the volume of extra vapor produced by the pumping effect e.g., vapor 19.1 and Tec 4 vaporizers.
- 3- By using a **pressurized valve which is inserted at the downstream of the vaporizer** to ensure that the pressure in the vaporizer is constant and greater than the pressure at the ventilator.
- 4- By inserting **one way (unidirectional) valve** at the outlet tube to minimize the pumping effect.
- 5- By constructing the **bypass chamber in the same volume of the vaporizing chamber** so that the gas in each is compressed or expanded equally.

Factors Affecting the Performance of Vaporizers (Factors Affecting the Output Vapor Concentration)

1- The Saturated Vapor Pressure (SVP):

A highly volatile anesthetic agent with high SVP e.g., diethyl ether is more volatile and is present in much higher concentration than those less volatile agents with low SVP e.g., halothane.

2- The Temperature:

The temperature of the liquid anesthetic in the vaporizer will determine the SVP, as heating increases vaporization while cooling decreases it.

3- The Splitting Ratio:

It is the ratio of the gas flow bypassing the vaporizer to the gas flow entering it. It determines the output vapor concentration as above.

4- The Surface Area of the Gas-Liquid Interface:

If the surface area of the gas-liquid interface is large e.g., by wicks or bubbling (as above), the efficiency of vaporization is improved.

If the surface area is small, the flow of gas through the vaporizing chamber may be too rapid to achieve complete saturation with anesthetic molecules with the gas above the liquid.

5- The Rate of Fresh Gas Flow:

The vaporizer output concentration is almost not affected by changes in fresh gas flow rates between 250 mL/min to 15 L/min (i.e., flow compensated).

At very low rates (< 250 mL/min), there is insufficient vaporization generated by the low fresh gas flow.

At very high flow rates (> 15 L/min), there is incomplete mixing of the fresh gas flow with the anesthetic vapor. In both cases, output vapor concentration is lower than the dial setting.

To solve this problem; the anesthetic agent is delivered into the gas stream through a fine nozzle i.e., the liquid anesthetic is injected into the output stream (figure 6-32). The rate of delivery of the anesthetic agent depends upon the pressure difference between P_1 and P_2 across the nozzle, and this is adjusted by the throttle valve. If flow through the vaporizer is increased, the pressure across the valve is increased and so, more anesthetic agent is delivered to maintain the same concentration. In this way, the vaporizer remains accurate despite changes in flow. The throttle valve is calibrated to indicate the percentage of anesthetic delivered.



Figure 6-32: Injection of liquid anesthetic agent

► The Pumping Effect:

If the vaporizer is used with intermittent positive pressure ventilation, the concentration of the output vapor is increased (see above).

► The Position of Vaporizers in Relation to a Circle System:

• A vaporizer may be placed either outside or inside a circle absorption circuit (figure 6-33). There are two possibilities:

	Vaporizer Inside Circuit (VIC)	Vaporizer Outside Circuit (VOC)
Position of the vaporizer	It lies in line of the patient's ventilation. The vaporizers have low internal resistance.	It lies in line of fresh gas flow as on the back bar of the anesthetic machines, because the vaporizers have high internal resistance.
Vaporization depends on	<ul style="list-style-type: none"> Fresh gas flow rate in contrast to the VOC. The inspired concentration is higher at low fresh gas flow rate because the expired concentration is diluted to a lesser extent. Minute volume of the patient. 	<ul style="list-style-type: none"> Fresh gas flow e.g., if fresh gas flow rate is < 1 L/min, the vaporization will be very small even if the vaporizer is set to deliver a high concentration, so the fresh gas flow rates should be increased. Efficiency of vaporizer.
Used safely with	Spontaneous respiration.	Controlled respiration.
Efficiency of the Vaporizer used	Low (and low resistance).	High.
Examples	Draw-over vaporizers as Goldman Vaporizer.	Plenum vaporizers as modern Tec vaporizer.

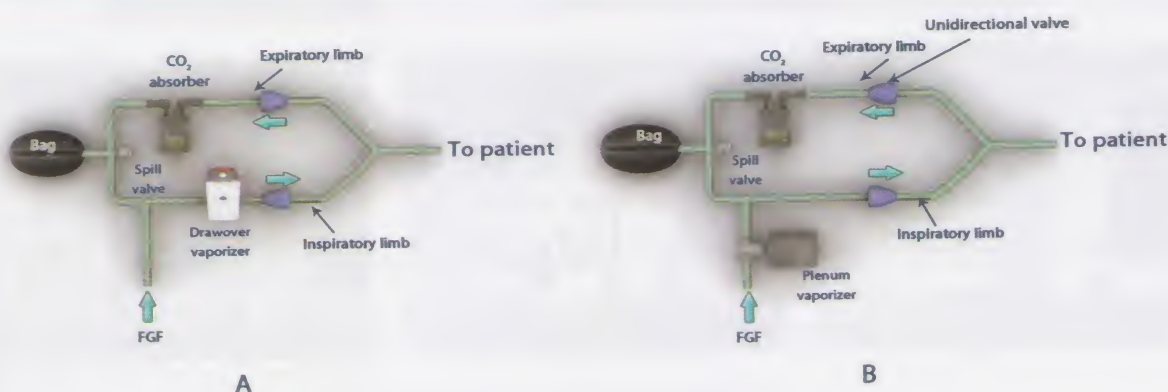


Figure 6-33: Position of vaporizer; VIC (A) and VOC (B)

• A vaporizer should be placed **between the flowmeter block and the emergency O₂ flush control**, so that there is no risk that the high flow of O₂ from the latter can be delivered through the vaporizer.

► The Barometric Pressure:

The SVP of the liquid anesthetic depends on the temperature but not on the barometric pressure. Therefore, the performance of the vaporizer is not affected by changes in barometric pressure.

For example, the performance of a variable bypass vaporizer (halothane or isoflurane) at high and low barometric pressures can be explained as follows:

	At 1 bar (100 kPa), 20°C e.g., at normal atmospheric pressure.	At 2 bar (200 kPa), 20°C e.g., in hyperbaric chamber.	At ½ bar (50 kPa), 20°C e.g., at high altitude.
SVP (kPa)	32	32	32
SVC (vol. %)	32% of the 100 kPa	16% of the 200 kPa	64% of the 50 kPa
When a vaporizer dial is set at 1%, the partial pressure at the outlet is	1% of 100 kPa i.e., 1 kPa	0.5% of 200 kPa i.e., 1 kPa	2% of 50 kPa i.e., 1 kPa
Density (g/mL)	2	4	1
Explanation		The SVC is halved, but the density is doubled, so the mass delivered to the patient remains constant.	The SVC is doubled, but the density is halved, so the mass delivered to the patient remains constant.

N.B.: The resistance to gas flow in the vaporizing chamber is directly proportional to the density of the vapor. This may produce some changes in the splitting ratio and the output vapor concentration.

Vaporizer Mounting Systems

Vaporizers are mounted on the back bar of the anesthetic machine, as many as three vaporizers can be mounted side by side. Mounting of vaporizers may be permanent or detachable:

Permanent Mounting:

It requires tools and a special technician to remove or install a vaporizer.

Detachable Mounting (Selectatec System):

It does not require tools or a special technician to be removed or installed (figure 6-34).

Selectatec is pronounced select-a-Tec i.e., select a Tec vaporizer.

It has the following **advantages**:

- It allows quick and easy removal or installation of any vaporizer by the user.
- It allows replacement of the vaporizer without interrupting the flow of the carrier gas.
- It allows the use of one vaporizer at any one time so prevents contamination of the downstream vaporizer by the upstream one.
- It allows the anesthetic machine to be more compact because few mounting locations are needed in the anesthetic machine.
- If malignant hyperthermia is a potential problem, the vaporizers can be removed and the machine is decontaminated by continuous flushing with oxygen. This gives better results than if the vaporizer remains on the anesthetic machine in the off position.



Figure 6-34: Selectatec system

N.B.: Excessive tilting of older vaporizers (Tec 4, Tec 5, and vapor 19.n) during transport may flood the bypass area with the liquid anesthetic and lead to dangerous high anesthetic concentrations.

Modern Vaporizers

They include:

- Tec series as Tec 3, Tec 4, Tec 5 and Tec 6 (which is specifically designed for desflurane).
- Vapor 19.n.
- The heated-chamber pulsed vaporizer.
- Aladin cassette vaporizer.

General Features:

They are summarized as follows:

- 1- They are concentration-calibrated or variable-bypass vaporizers.
- 2- They are flow-over (plenum) vaporizers.
- 3- The vaporization is improved by using wicks.
- 4- The cooling effect is minimized by thermal compensation (Temperature compensated "Tec series" vaporizers) either by automatic or computerized mechanisms.
- 5- The pumping effect is minimized by several mechanisms (as above).
- 6- **They are classified as** vaporizer outside circuit (VOC).

Safety Features:

- 1- They are **agent specific** and **do not allow misfilling** i.e., each vaporizer should be specific for only one agent for which it is designed and calibrated. This is achieved by an agent specific key-filling device

Figure 6-35). Unintentional misfilling by a wrong agent may lead to underdosing or overdosing e.g., when enflurane-specific vaporizer is filled with halothane, overdose may be produced because:

- Halothane's higher SVP, 243 mmHg, versus 175 mmHg of enflurane will cause a 40% greater amount of anesthetic vapor to be released.
- Halothane is more than twice as potent as enflurane.

Conversely, filling a halothane vaporizer with enflurane will cause anesthetic underdosing.

There are also a color code for each anesthetic gas on the vaporizer and the bottle's label; halothane (red), isoflurane (violet), enflurane (orange), sevoflurane (yellow), and desflurane (blue).

3- They **do not allow overfilling** because the filler port of the vaporizer is located at the maximum safe level of the liquid anesthetic.



Figure 6-35: An agent-specific connector for vaporizer filling; two different isoflurane connectors (left and middle) and a sevoflurane connector (right)

3- They **do not allow cross-filling or trans-filling**. When two vaporizers are arranged in series (side by side), the downstream vaporizer will be contaminated by the agent in the upstream vaporizer. This is prevented by the use of a **selectatec or an interlock mechanism** that prevents the concurrent use of more than one vaporizer at a time.

4- They **do not allow leaks from the vaporizer** to the circuit. The vaporizer control knob should be standardized to turn "off" in a clockwise direction, when the vaporizer is in the off position. Both the inlet and outlet ports to the vaporizing chamber should be occluded to avoid contamination of gas from the flowmeters with traces of anesthetic.

Desflurane Vaporizer (Tec 6)

It is an electrically heated and pressurized vaporizer. Modern vaporizers (such as Tec 4, Tec 5 and vaporizer series) are unsuitable for use with desflurane because desflurane has unique physical properties:

- Its boiling point (22.8°C) is near room temperature.
- Its vapor pressure (669 mmHg) is near one atmosphere.
- Its potency is low (MAC is 6-9%) which is about 1/5 of the potency of other volatile agents and the maximum vaporizer output is 22 (unlike halothane and isoflurane 5, and sevoflurane 8). Therefore, more vaporization is required which in turn causes more cooling that would overwhelm the ability of conventional vaporizers to maintain a constant temperature (figure 6-36).

Desflurane vaporizer contains a **desflurane reservoir (desflurane sump)** which is:

- Heated by an **electrical heater** and controlled at 39°C by an **electrical thermostat**.
- Pressurized with a built-in **pressure regulator** to keep the pressure at 1500 mmHg. The signals from the pressure regulator (transducer) are processed electronically and used to adjust a valve upstream of the transducer to keep the pressure across the transducer constant whatever the fresh gas flow is. This keeps the concentration of the output vapor constant.

This means that the vaporizer is **heated to double the room temperature and pressurized to double the atmospheric pressure**.

The performance of desflurane vaporizer Tec 6 is affected by two factors:

- High altitude: because the ambient pressure will be low. This affects the pressure in the pressurized chamber. Therefore, the partial pressure of the agent is decreased.
- Carrier gas composition: The output decreases when the carrier gas composition is changed from 100% O₂ to 30% O₂ and 70% N₂O. The decrease may be 20% especially at low flow rates.

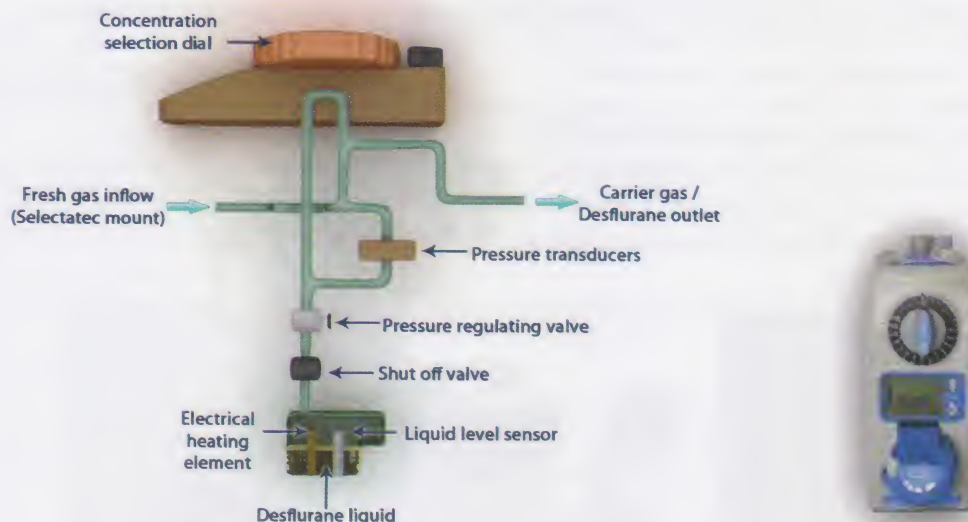


Figure 6-36: Desflurane vaporizer

Because desflurane has a high SVP (669 mmHg), misfilling of other vaporizers with this agent may cause desflurane overdose. Therefore, there is a unique agent-specific filler cap of desflurane bottle to prevent its use in other vaporizers.

Because desflurane has a low boiling point, the filler cap of the desflurane bottle makes a tight seal with the filler port of the vaporizer to prevent loss of desflurane to the atmosphere during the filling process.

The Heated-Chamber Pulsed Vaporizer

- The anesthetic agent chamber is pressurized e.g., to 0.4 bar which transfers the anesthetic agent to a heated chamber. The temperature at the top of the chamber is accurately controlled by means of a heater and a thermistor temperature sensor (figure 6-37).

- If the pressure and temperature are constant, the number of moles per unit volume is fixed, according to the ideal gas equation as $PV = nRT$.

So, after rearrangement of the equation $n/V = P/RT$.

- A solenoid valve at the top of the vaporizing chamber alternately opens and closes. During the fixed opening period, a given volume, thus a given number of moles of the anesthetic agent, is added to the flow of fresh gas. The concentration of anesthetic agent leaving the vaporizer is controlled by the frequency by which the valve is opened.

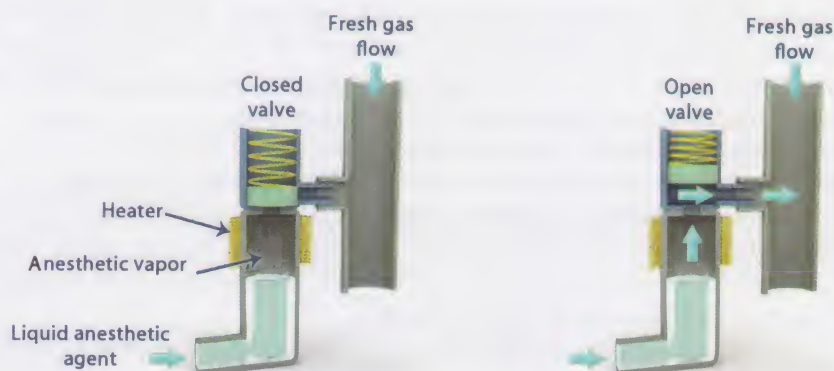


Figure 6-37: Heated-chamber pulsed vaporizer

- The vaporizer can only be used with a system that measures the fresh gas flow and produces an electronic output. This is then used to control the frequency at which the vaporizer valve is pulsed and hence maintain the desired vaporizer output concentration if the fresh gas flow is changed.

Aladin Cassette Vaporizer

- Gas flow from the flow control is divided into bypass flow and liquid chamber flow (figure 6-38). The latter is conducted into an agent-specific, color-coded, detachable cassette (Aladin cassette) in which the volatile anesthetic is vaporized.
- The machine accepts only one cassette at a time and recognizes the cassette through magnetic labeling.
- The cassette does not contain any bypass flow channels; therefore, unlike traditional vaporizers, liquid anesthetic cannot escape during handling and the cassette can be carried in any position.
- After leaving the cassette, the anesthetic-saturated liquid chamber flow reunites with the bypass flow before exiting the fresh gas flow.
- The concentration of the output vapor is adjusted by turning an agent wheel which controls, by a preset computer software, the number of output pulses from the agent wheel.

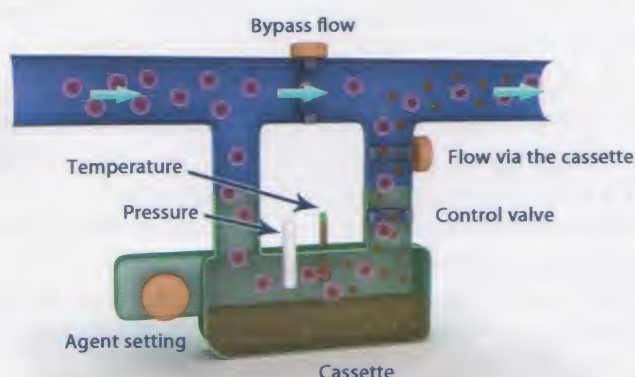


Figure 6-38: Aladin vaporizer

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Care of Vaporizers

- 1- **Frequent vaporizer calibration** is recommended by the manufacturers. It is performed by a refractometer or anesthetic gas monitor.
- 2- **Frequent vaporizer evacuation** is recommended at regular intervals about **1-2 weeks**, in case of halothane, to prevent accumulation of thymol (a preservative) which is concentrated after the halothane is vaporized. If thymol reaches the lung in high concentration, it causes pulmonary injury.

PART 5: ANESTHETIC BREATHING SYSTEMS (CIRCUITS)

Definition

Anesthetic breathing systems are the connection and link between the anesthetic machine and the patient. They have the following functions:

- Adequate supply of oxygen to prevent hypoxia.
- Adequate supply of the anesthetic concentrations (already set by the vaporizer) to prevent awareness or over-dosage.
- Adequate removal of exhaled CO_2 by preventing rebreathing to maintain normocapnia.

Classifications

Unfortunately, there is no international standard for the classification of anesthetic breathing systems. Even the word "system" is not universal as some use the word "circuit" instead.

The term "system" is preferred in the classification as only in the closed system does the breathed gas complete a circuit.

There are three classifications of breathing systems:

- 1- Functional classification.
- 2- Technical classification.
- 3- Combined functional and technical classification (Mapleson systems).

1- Functional Classification:

This is based on the boundary of the breathing system that restricts entry of fresh gas into the system, or provides venting of expired gas from the system. It includes:

- **Open system:** unbounded system with no restriction on fresh gas entry.
- **Semi-open system:** partially bounded system with some restriction on fresh gas entry.
- **Closed system:** fully bounded system with no provision for gas venting.
- **Semi-closed system:** partially bounded system with provision for excess gas venting.

This classification is **not preferred** because there is confusion especially in the terms "semi-open" and "semi-closed" where in the UK, systems such as the Magill, which are neither closed nor open, are often referred to as "semi-closed"; however, in the USA, the term "semi-open" is used instead, and the term "semi-closed" is used for the closed system with leak.

2- Technical Classification:

This is based on the design of the system. It includes:

a) Re-Breathing Systems with CO₂ Absorption:

There is mixing of expired gas with fresh gas. This mixture is re-breathed by the patient after chemical absorption of CO₂ by soda lime or baralyme. They include:

1- To and Fro or Single-Phase Systems:

In which gases pass through the CO₂ absorber during both inspiration and expiration.

2- Circle or Two-Phase Systems:

In which gases pass through the CO₂ absorber through two separate inspiratory and expiratory tubes with unidirectional valves to ensure one-way flow of gases.

b) Non-Rebreathing Systems:

The expired gas containing CO₂ is removed and replaced by fresh gas. They include:

1- Valve-Controlled Systems (Draw-Over Systems):

Idea:

In which the expired gas is discharged from the system through a non-rebreathing one-way valve.

These systems use draw-over vaporizers (see before "Vaporizers").

The valve (e.g., Ambu E valve) contains **moulded silicone rubber one-way inspiratory and expiratory valves** (figure 6-39). They allow patient's inspiration through one connection and expiration through the other connection. During inspiration, the inspiratory valve opens while the expiratory valve closes (the reverse occurs during expiration). This prevents rebreathing. It can be used during spontaneous and controlled ventilation.



Figure 6-39: Ambu E valve

Uses:see before in "Vaporizers".

Advantages:

- Simple.
- Robust.
- Usable with any agent.

- Portable.
- Low resistance to gas flow.
- Controllable vapor output.

Disadvantages:

- 1- Poor control of inspired gas concentration and depth of anesthesia.
- 2- Because of absence of the reservoir bag in some types, the depth of tidal volume is not well appreciated during spontaneous ventilation.
- 3- There is no conservation of exhaled heat or humidity.
- 4- There is pollution of the operating room with a large volume of waste gas.

N.B.: Resuscitation Breathing Circuits:

For example, AMBU bags or the Laerdal resuscitator (figure 6-40).

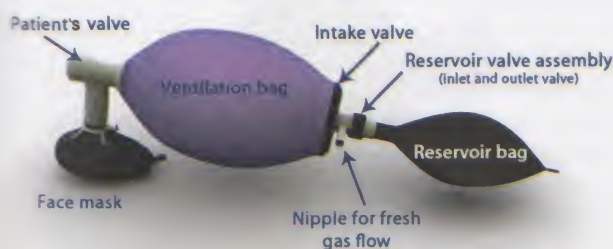


Figure 6-40: The Laerdal resuscitator

Advantages: It is simple and portable. A self inflating bag can deliver 40-60% O₂ even when 100% O₂ is flowing into the bag; therefore, there must be a **second reservoir plastic bag** which will fill with 100% O₂ during the patient exhalation phase and so can deliver **O₂ concentration up to 100%**.

Components:

- A **non-rebreathing valve (patient's valve)**: allows unidirectional flow of the gas from the bag to the patient.
- A **ventilation bag**; which is compressible and self-inflating. It is filled by an O₂ source connected to fresh gas flow nipple, from room air or from the O₂ in the reservoir bag.
- A **reservoir bag**; which is filled with O₂ from the O₂ source.
- A **reservoir valve assembly**; which is formed from two unidirectional valves:
 - The **inlet valve** that allows ambient air to enter the ventilation bag if the fresh gas flow is inadequate to maintain reservoir filling.
 - The **outlet valve** that allows excessive fresh gas flow to be vented from the ventilation bag to the outside when positive pressure is applied to the bag.

Disadvantages: It needs a high fresh gas flow to achieve a high FiO₂.

2- Flow-Controlled Systems:Idea:

in which the expired gas is displaced from the system by an adequate fresh gas flow, and then discharged through the expiratory valve.

a Systems without a Gas Reservoir:

They are open systems. The absence of a fresh gas reservoir allows uncontrolled entry of atmospheric air resulting in marked changes in the concentration of inhaled anesthetics. They include:

1- Insufflation Method:Idea:

The anesthetic gases **blow over the patient's face** by one of the following means:

- **Without direct connection** between a breathing circuit and a patient's airway, or through a **cupped hand** containing the end of the gas delivery tube (figure 6-41).
- An **Edinburgh mask** (obsolete) where the anesthetic gases reach the mask by a side opening and the patient's expiration occurs through a wide opening to room air. It produces a negligible increase in the respiratory dead space.

- A mouth cannula that carries the anesthetic gases to the side of the patient's mouth using a special gag device.
- A nasal cannula through the patient's nostrils.
- Simple O₂ mask.
- Venturi O₂ mask.

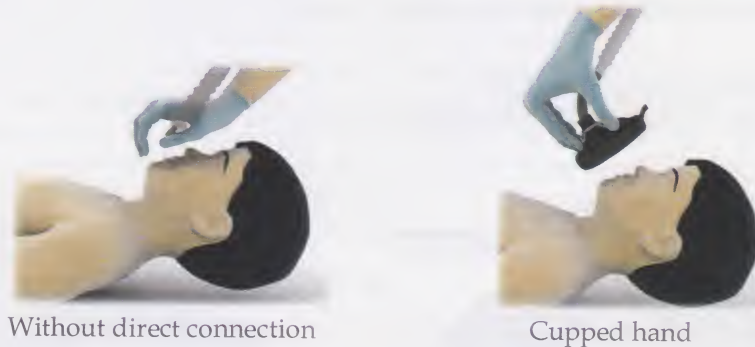


Figure 6-41: Insufflation methods

Advantages:

There is **usually no rebreathing** of exhaled gases especially if the flow is high enough because there is no resistance to the patient's breathing, as there is no or minimal contact with the patient.

Disadvantages:

- There is **poor control of the patient's ventilation and concentrations of O₂ and other gases** received by the patient because there is always air dilution.

N.B.: During peak forced inspiration, the peak inspiratory flow may reach up to 50 L/min, but as the flow from the flowmeters is usually low (from 2-15 L/min), so air dilution is high during inspiration. In Venturi mask, the flow of gas (O₂ and entrained air) exceeds the peak inspiratory flow; therefore, a constant concentration of O₂ is delivered.

- There is **no conservation of exhaled heat or humidity**.
- There is pollution of the operating room with a large volume of waste gas.

Uses:

- During induction in pediatric anesthesia with inhalation anesthetics especially by cupped hand method because children often resist the placement of a face mask or an intravenous line.
- During O₂ supply in the operating room, post-anesthetic care units, and intensive care units to maintain arterial oxygenation.

2- Open Drop Method:

Idea: (it is of historical importance and not used now).

A highly volatile anesthetic, most commonly ether or halothane, is dripped onto a gauze-covered mask (**Schimmelbusch mask**) applied to the patient's face. As the patient inhales, air passes through the gauze, vaporizes the liquid agent, and carries high concentrations of anesthetic to the patient. It is a type of draw-over vaporization as it depends on the patient's inspiratory efforts to draw ambient air (no need for a source of O₂ supply).

3- Combined Functional and Technical Classification (Mapleson Classification)

In 1954, **Mapleson** classified anesthetic breathing systems into 5 types (**A, B, C, D, and E**). The Mapleson E was modified by **Jackson Rees**, and was classified as the Mapleson F system.

There are two co-axial systems which are modifications of Mapleson systems. They include:

- **Lack co-axial system** (modified Mapleson A, rarely used).
- **Bain co-axial system** (modified Mapleson D, commonly used).

Mapleson systems are considered:

- **Semi-closed** by functional classification, because they allow venting of excess gas.
- **Flow-controlled non-rebreathing** systems by technical classification, because they depend on an adequate fresh gas flow for displacing the expired gas from the system thus preventing rebreathing and maintaining normocapnia.

Components of Mapleson Systems:

A) Breathing Tubes:

It is made of: - **rubber** (reusable, but not autoclavable). It is black in color due to its high carbon content to allow escape of static electricity i.e., antistatic.
 - **silicon** (reusable, and autoclavable). It is expensive.
 - **plastic** (disposable).

Shape: is **corrugated** to avoid its closure during kinking.

Diameter: is **wide** (usually 22mm) to create a low-resistance pathway.

Volume: should be a large volume, at least **equal the patient's tidal volume**, to act as a reservoir for anesthetic gases. Very large volumes are avoided to decrease the fresh gas flow requirements.

Compliance (Δ volume / Δ pressure):

It is very important during positive mechanical ventilation.

High compliance tubes make an increased difference between the volume of gas delivered to a circuit by a reservoir bag or ventilator and the volume actually delivered to the patient.

The compliance of the standard adult breathing circuit is 5 mL gas/cm H₂O.

The compliance of the standard pediatric breathing circuit is 1.5-2.5 mL gas/cm H₂O.

For example, if a breathing circuit with a compliance of 7 mL/cm H₂O is pressurized, during delivery of a tidal volume, to 20 cm H₂O, 140 mL (7 x 20) of the tidal volume will be lost to the circuit due to tube expansion.

B) Fresh Gas Inlet:

It is the site where continuous entering of anesthetics and O₂ from the anesthetic machine to the breathing system occurs.

Its position in the breathing circuits is an important factor in differentiating Mapleson circuit from other types.

C) Adjustable Pressure-Limiting Valve (APL Valve):

Other names: **Pressure-Relief Valve, Pop-off Valve, Spill Valve, Heidbrink Valve, and Expiratory Valve**

Function:

It allows gases to exit the circuit when there is a positive pressure within the system to control the pressure inside the circuit. Exiting waste gases are then delivered to the operating room atmosphere or scavenging system. It prevents damage of the patient's lung.

Description: There are many types but the most common is described (figure 6-42):

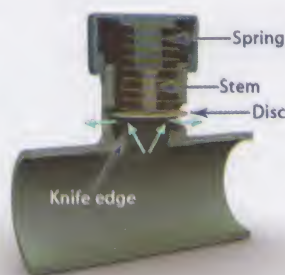


Figure 6-42: Spill valve

It comprises the following parts:

- A **light-weight disc** which rests on a knife edge seat to minimize the area of contact and reduce the risk of adhesion resulting from surface tension of condensed water.
- A **stem** which is connected to the disc to act as a guide to position the disc correctly.
- A **light spring** is incorporated in the valve so that the pressure required to open the valve may be adjusted.

State of the Valve:

- It should be **fully open** i.e., low tension of the spring and low resistance occur during **spontaneous ventilation** as expiration will generate positive pressure which in turn pushes the disc up and opens the valve. The resistance to expiration should be very minimal (1-5 mmHg).

- It should be **partially closed** i.e., screwed down to increase the tension in the spring during **assisted manual ventilation** by reservoir bag compression to produce controlled escape of the gas during the inspiratory phase.
 - It should be **closed** i.e., high tension of the spring and high resistance are present during **controlled mechanical ventilation** by a ventilator to avoid any leak in the circuit (the ventilator exhaust valve is the one that allows gases to exit to outside the circuit).
- When the valve is **left unintentionally closed**, fresh gas flow continues to enter into the circuit; the valve should **open at a peak pressure, usually 40-60 cm H₂O**, to avoid barotrauma to the patient's lungs.

D) Reservoir Bag (Breathing Bag):

Function: It acts as: • a reservoir of anesthetic gases
and • a method of generating positive pressure ventilation.

Compliance: It is designed to increase in compliance when its volume increases.

The reservoir bag is highly distensible and rarely reaches pressures above 60 cm H₂O.

The volume of the reservoir bag is determined by the fresh gas flow (FGF) and the adjustment of the spill valve.

Three phases are present during its filling:

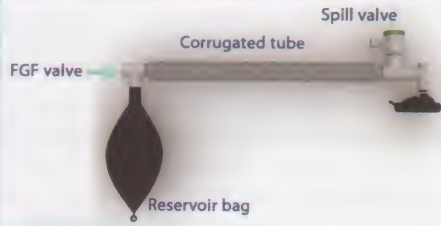
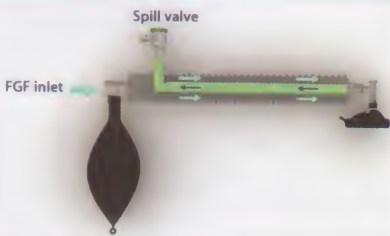
Phase I: At the start of bag filling the **pressure is minimal** until the bag is filled up to its capacity e.g., 0.25, 0.5, 1, 2, or 3 liters.




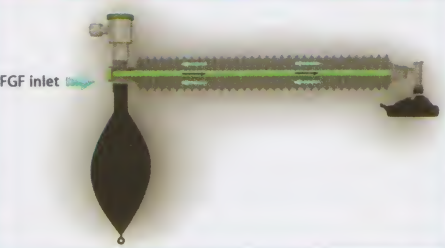
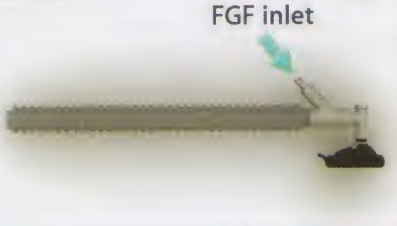
Phase II: The pressure **increases rapidly** to a peak.


Phase III: The pressure reaches a **plateau or even a slight decrease** occurs, due to opening of the pressure-relief valve to avoid barotrauma of the patient's lungs, if the valve is unintentionally left in the closed position as above.

Types of Mapleson Systems

Mapleson A (and Lack system), B, C, D (and Bain system), E and F are shown in figures 6-43, 44, 45, 46, 47, 48, 49, and 50.

Mapleson System	Description	Required Fresh Gas Flow		Efficiency	
		Spontaneous	Controlled	Spontaneous	Controlled
A (Magill system) By Sir Ivan Magill in 1920	 <p>Figure 6-43</p>				
	The FGF inlet and reservoir bag are away from the patient. The spill valve is close to the patient.	1 x MV Actually the system can work with less FGF, but in practice, higher flow is selected to compensate for leaks.	2-3 x MV	The most efficient It is still used in adults.	The least efficient
Lack system (Coaxial Magill system)	 <p>Figure 6-44</p>				
	It has two tubes with the same axis; a wide outer tube (22 mm diameter) through which inspiration occurs, and a narrow inner tube (7 mm diameter) through which expiration occurs, so resistance to expiration may occur.	1 x MV	2-3 x MV	As "A" system	

						
	Figure 6-45					
	The bag is away from the patient. The FGF inlet and the spill valve are close to the patient.	2-3 x MV	2-3 x MV	The least efficient. It is rarely used in clinical practice.	Inefficient	
						
	Figure 6-46					
	- The bag, FGF inlet, and the spill valve are close to the patient as there is no corrugated tube.	2-3 x MV	2-3 x MV	The least efficient. It is rarely used in clinical practice.	Inefficient	
						
	Figure 6-47					
	- The bag and spill valve are away from the patient. - The FGF inlet is close to the patient.	2-3 x MV	1 x MV	Inefficient	The most efficient It is used in adults.	
						
	Figure 6-48					
	It has two tubes with the same axis; a wide outer tube (22 mm diameter) through which expiration occur, and a narrow inner tube (7 mm diameter) through which inspiration occurs.	200-300 mL/kg/min	70-80 mL/kg/min	As "D" system It is a modified "D" system.		
						
	Figure 6-49					
	The FGF inlet is close to the patient (no bag or valve are present) It is an unmodified T-piece.	2-3 x MV	2-3 x MV	Efficient	Efficient	

F (Jackson-Rees' modification of the Ayre's T-piece)	 <p>Figure 6-50</p> <p>The bag is away from the patient. The FGF inlet is close to the patient. (There is no valve).</p>	2-3 x MV	2-3 x MV	Efficient. It is the one mainly used in pediatrics.	Efficient. It is the one mainly used in pediatrics.
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N.B.: MV = Minute ventilation = 70-80 mL/kg /min.

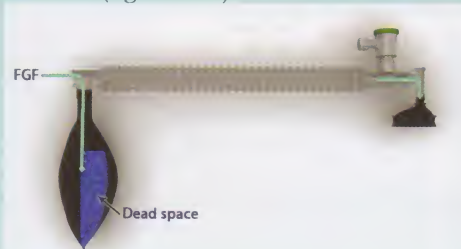
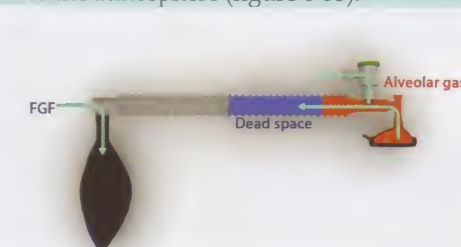

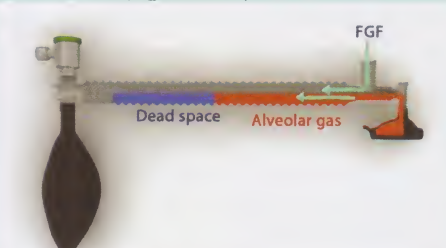
FGF = Fresh gas flow

FG = Fresh gas

Efficiency of Mapleson Systems:

The efficiency is measured by the amount of fresh gas flow required to eliminate, as much as possible, CO₂ rebreathing. As these circuits do not contain any unidirectional valves or CO₂ absorber, there is usually some rebreathing in any Mapleson circuit. To attenuate this rebreathing, high fresh gas flow is required, the higher the flow required, the less the efficiency.

Mechanism of Action of Mapleson Systems

Mapleson "A" System (Magill System)	Mapleson "D" System
<p><u>A) During spontaneous ventilation:</u> <u>During inspiration:</u></p> <ul style="list-style-type: none"> - Gas is inhaled from the corrugated tube and the bag as they contain FG and expired dead space gas (contains no CO₂), so this system can be used at a FGF of even 70% of the patient's minute ventilation (figure 6-51).  <p>Figure 6-51</p> <p><u>During expiration:</u></p> <ul style="list-style-type: none"> - During the initial part of the expiration, the reservoir bag is not full and thus the pressure in the system does not increase, so that the first part of the exhaled gas (which is the dead space gas containing no CO₂) will pass along the corrugated tube towards the bag and will not exit through the spill valve. Therefore, the bag is filled by the dead space gas and the FG from the anesthetic machine. - During the late part of expiration, the bag becomes full, the pressure in the system increases and so, the spill valve opens (usually at 0.5 cmH₂O pressure), venting all subsequent exhaled alveolar gas to the atmosphere (figure 6-53).  <p>Figure 6-53</p> <p><u>During the expiratory pause:</u></p> <ul style="list-style-type: none"> - When FGF is sufficiently high and continues to flow from the anesthetic machine to the system, it pushes all the remaining 	<p><u>A) During spontaneous ventilation:</u> <u>During inspiration:</u></p> <ul style="list-style-type: none"> - The patient inhales FG and some of the expired dead space gas and expired alveolar gas (with CO₂) according to the FGF (figure 6-52).  <p>Figure 6-52</p> <p><u>During expiration:</u></p> <ul style="list-style-type: none"> - Exhaled dead space gas, exhaled alveolar gas, and FG, mix in the corrugated tube and travel towards the bag where the bag starts to fill (the exhaled dead space gas starts to fill the bag at first). - When the bag is full, the pressure in the system increases, the spill valve opens and the mixture of gases (dead space, alveolar and FG) is vented to the outside (figure 6-54).  <p>Figure 6-54</p> <p><u>During the expiratory pause:</u></p> <ul style="list-style-type: none"> - When FGF continues to flow from the anesthetic machine to the system, it pushes the exhaled alveolar gas (with CO₂) along the corrugated tube to be vented through the spill

exhaled alveolar gas (with CO_2) distally along the corrugated tube to be vented through the spill valve before the next inspiration. Therefore, no rebreathing occurs (figure 6-55).



Figure 6-55

B) During controlled manual ventilation:

During controlled inspiration:

It is produced by the anesthesiologist squeezing the reservoir bag while the spill valve is partially closed. Pure alveolar gas (contains CO_2) reenters the patient's lung and is followed by a mixture of FG, dead space gas, and alveolar gas which in turn re-enters the patient's lung too. When the pressure in the system increases, it will open the spill valve venting this mixture also to the outside.

Therefore, rebreathing occurs. To avoid this, FGF must be sufficient and high enough to vent gas from the system and to inflate the patient's lung ($2-3 \times \text{MV}$) (figure 6-57, a and b).

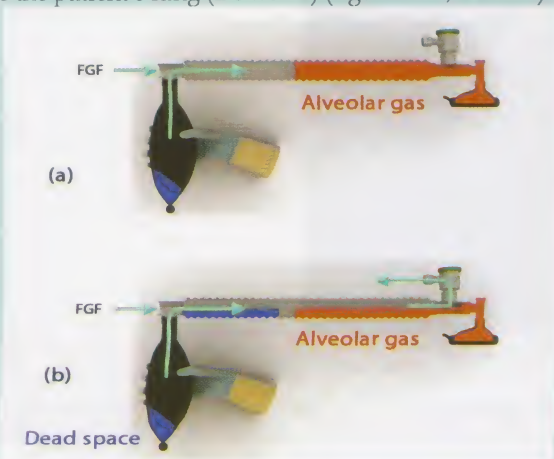


Figure 6-57

During expiration:

Exhaled dead space gas (without CO_2) and alveolar gas (with CO_2) pass along the corrugated tube and are likely to reach the partially full bag (from the previous squeezing by the anesthesiologist during previous inspiration) i.e., the bag is now filled with a mixture of FG, dead space gas, and alveolar gas. The exhaled alveolar gas does not exit through the spill valve because it is partially closed to allow the gases to reach the patient's lung during the next controlled inspiration (figure 6-60).



Figure 6-60

During the expiratory pause: (if it is incorporated into the

valve before the next inspiration, but some of the alveolar gas is still in the corrugated tube and is inhaled in the next inspiration so rebreathing occurs. To avoid this, the FGF must be $2-3 \times \text{MV}$ (at least 12 L/min in an adult) (figure 6-56).

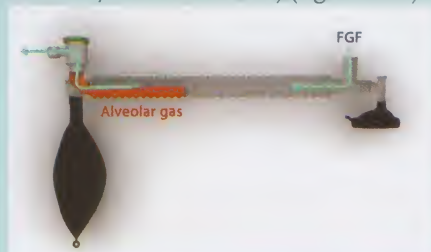


Figure 6-56

B) During controlled manual ventilation:

During controlled inspiration:

It is produced by the anesthesiologist squeezing the reservoir bag while the spill valve is partially closed. The FG and minimal exhaled gas enter the patient's lung. When the pressure inside the system increases, the spill valve opens and a mixture of the FG and the alveolar gas is vented. Therefore, no rebreathing occurs and so the FGF can be $1 \times \text{MV}$ (figure 6-58).



Figure 6-58

During expiration:

Exhaled dead space gas (without CO_2), alveolar gas (with CO_2) and FG pass along the corrugated tube and are likely to reach the partially full bag (from the previous squeezing by the anesthesiologist during previous inspiration) i.e., the bag is now filled with a mixture of FG, minimal dead space gas, and minimal alveolar gas where the exhaled alveolar gas exits through the spill valve (figure 6-59).



Figure 6-59

During the expiratory pause: (if it is incorporated into the ventilatory cycle) FG fills the corrugated tube and the bag where it may dilute the exhaled gas present. Presence of the expiratory pause increases the efficiency of the Mapleson "D" system.

ventilatory cycle)

FG fills the corrugated tube and the bag where it may dilute the exhaled gas present.

Disadvantages of Mapleson "A":

1- The system increases the apparatus dead space which extends from the anesthetic facemask to the spill valve (it is about 100 mL). This apparatus dead space is added to the patient's dead space. Therefore, Mapleson "A" system is not used in pediatrics < 4 years of age.

(N.B.: Dead space is the space through which inspiration and expiration occur without gas exchange. It can occur inside the body "from the nasopharynx up to the terminal bronchioles before the respiratory bronchioles" and can occur outside the body as the apparatus dead space).

2- It is heavy and unsuitable during head and neck surgery especially when a scavenging system is used because the spill valve is attached close to the patient. Lack coaxial modification permits the spill valve to be away from the patient.

Bain System

It is a modified Mapleson "D" system. It is the most commonly used coaxial system.

Description: see above (figure 6-61).



Figure 6-61: Bain circuit

Advantages:

- 1- **Warming** of the inspired gases in the inner tube by the surrounding warm expired gases in the outer tube.
- 2- Improved **humidification** of inspired gases due to partial rebreathing.
- 3- **Easy scavenging** of the waste gases because the expiratory valve is away from the patient.
- 4- The length and light weight allow the anesthesia machine to be removed away from the patient **during head and neck surgery**.
- 5- Some types of **automatic ventilators** e.g., Penlon Nuffield 200 can be connected to the Bain system by a one-meter length of corrugated tubing. The tube is placed instead of the bag and the spill valve is kept closed completely.

During inspiration, the gas from the ventilator pushes a mixture of ventilator fresh gas and alveolar gas from the corrugated outer tube of the Bain system into the patient's lung.

During expiration, the ventilator fresh gas and some of the alveolar gas are vented through the exhaust valve of the ventilator.

To prevent rebreathing, FGF should be 70-80 mL/kg/min (to maintain normocapnia) or 100 mL/kg/min (to cause moderate hypocapnia).

Disadvantages:

- 1- **A large waste of gases** is produced due to high FGF (200-300 mL/kg/min) **during spontaneous ventilation**.
- 2- **Kinking of the inner tube** prevents inhalation of FGF.
- 3- **Unrecognized disconnection or cutting of the inner tube** causes a large apparatus dead space and marked rebreathing of the exhaled gases. Therefore,
 - The outer tube should be transparent to allow inspection of the inner tube.

- Occlusion test should be performed before use; the system should be tested by occluding the distal end of the inner tube transiently with a finger or with the plunger of a 2-mL syringe while the FG flows to the system. There should be a reduction in the flowmeter bobbin reading during occlusion and an audible release of pressure when occlusion is disconnected.

⚡ **Movement of the reservoir bag during anesthesia does not indicate that FG is delivered to the patient** because the bag is connected to the outer expiratory tube.

Mapleson "E" System (Ayre's T-piece)

It acts in a similar manner to the Mapleson "D" system (figure 6-62).

During Expiration:

The corrugated tube fills with a mixture of exhaled and fresh gas where the dead space is present at the distal end (area A), the exhaled alveolar gas at (area B), and then the FG at (area C).

During the Expiratory Pause:

Only the FG will fill the proximal corrugated tube and dilutes and pushes the exhaled gases to be vented to the outside from the end of the tube especially if FGF is $2-3 \times MV$ (with a minimum 4 L/min) and so that rebreathing does not occur.

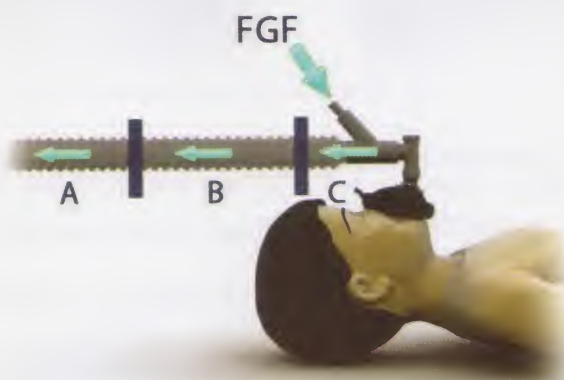


Figure 6-62: Mapleson "E" system

During Inspiration:

At first, the patient inhales gas from the FG coming from the inlet. When the patient's inspiratory flow becomes greater than the flow of fresh gas from the inlet of the T-piece, the patient may in addition draw and inhale from the gas in the proximal end of the reservoir tubing (area C).

Provided there is an expiratory pause (where the FG fills larger area of the corrugated tube), the possibility of rebreathing is decreased.

If the FGF is too low e.g., $< 2 \times MV$, the patient will draw upon the gases at area B and C, and rebreathing occurs.

If the corrugated tube is too small, the patient will inhale room air, thus the volume of the corrugated tube (which acts as a reservoir limb) should exceed the patient's tidal volume.

During Spontaneous Ventilation:

There is no indication of the presence or the adequacy of ventilation. Some anesthesiologists attach a visual indicator such as a piece of tissue paper or a feather, at the end of the corrugated tube, but this is not satisfactory enough.

During controlled ventilation:

Controlled ventilation is done by occlusion of the end of the corrugated tube with a finger. However, there is no way of assessing the pressure in the system and there is a possibility of exposing the patient's lungs to excessive volumes and barotrauma.

Mapleson "F" System (Jackson Rees' Modification of the Ayre's T-Piece)

The Ayre's T-piece (Mapleson E) was modified by Jackson Rees, where a small bag (0.5 L) with an open end was attached to the outlet of the reservoir limb (there was no valve present). Later on, a valve was added as a further modification (figure 6-63). It is suitable for children < 20 kg body weight.



Mapleson F without a valve



Figure 6-63: Mapleson F with and without a valve

Advantages:

- 1- The bag's movement indicates that the child is breathing during spontaneous respiration i.e., it acts as a **visual monitor** for spontaneous breathing.
- 2- By occluding the open end of the bag temporarily, it is possible to **confirm that fresh gas is entering the system**.
- 3- It provides a degree of continuous positive airway pressure (**CPAP**) during spontaneous ventilation and positive end expiratory pressure (**PEEP**) during mechanical ventilation.
- 4- It provides a convenient method of **assisted or controlled ventilation**. The open end of the reservoir bag is occluded between the 4th and the 5th fingers and the bag squeezed between the thumb and index fingers; the 4th and 5th fingers are relaxed during expiration to allow gas to escape from the bag. It is possible for an experienced anesthesiologist to assess (approximately) the inflation pressure and to detect changes in the lung and chest wall compliance.

Mapleson ADE System

This system consists of:

- Two parallel corrugated **tubing** of 15-mm diameters.
- The **Humphrey block** consists of an **APL valve**, a **lever** to select spontaneous or controlled ventilation, a **reservoir bag**, a **port** to connect a ventilator, and **safety pressure relief valve** which opens at a pressure above 6-kPa.
- The tubes are connected from one end to a **Y-piece connection** and from the other end to the Humphrey block (figure 6-64).

This system carries the properties of the Mapleson A, D, and E systems:

- When the lever is in the "A" mode (up), the system behaves as the Mapleson "A" and becomes connected to the bag where one tube acts for inspiration while the other for expiration (connected to APL and scavenging system). Now it can be efficiently used for spontaneous ventilation.
- When the lever is in the D/E mode (down), the inspiratory limb delivers gas to the patient while the expiratory limb returns it back. The Humphrey block acts as a reservoir and is open to atmosphere or connected to the ventilator such as Penlon. The bag and APL valve are now isolated from the system. It can be used now efficiently for mechanical ventilation.

In adults, FGF is 50-60 mL/kg for spontaneous ventilation,
and 70 mL/kg/min for mechanical ventilation.

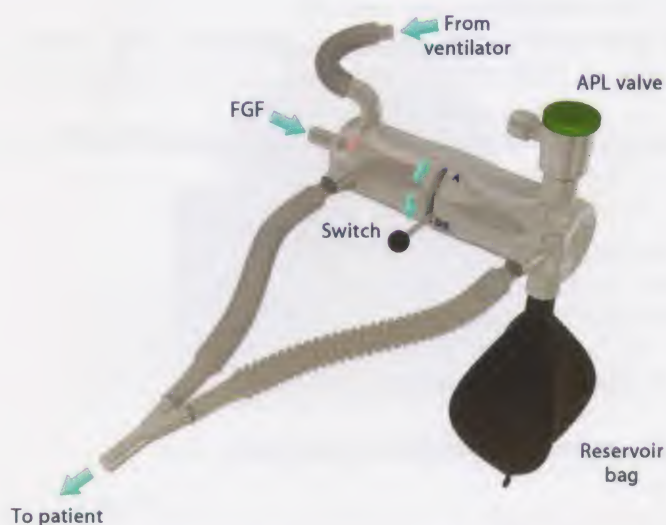


Figure 6-64: Mapleson ADE system

To-and-Fro (Waters') System

It is one phase rebreathing system. It is rarely used nowadays.

Components:

- A Mapleson C breathing system.
- A canister of soda lime; interposed between the spill valve and reservoir bag (figure 6-65).



Figure 6-65: To-and Fro system

Disadvantages:

- 1- The soda lime granules nearest to the patient become exhausted first, increasing the dead space of the system.
- 2- The canister is positioned horizontally and gas may be channelled above the soda lime unless the canister is tightly packed.
- 3- The system is cumbersome.
- 4- There is a possibility of inhalation of soda lime dust from the canister by the patient.

The Circle System

Types:

- **Semi-closed system**, if the FGF equals the minute volume (i.e., 6 L/min)
- **Low-flow system**, if the FGF is less than half the minute volume (i.e., less than 3 L/min).
- **Closed system**, if the FGF equals the gases (O_2 and anesthetic) taken up or consumed by the patient (i.e., 1 L/min or less).

The main difference between a low-flow and a closed circuit is the volume of fresh gas flow (FGF) per minute.

Both the low-flow and closed systems require:

- A **tightly closed circuit** which is achieved by closing the APL valve.
- **Continuous addition of O_2** to the system to replace the patient's metabolic uptake (250 mL/min).
- **Absorption of CO_2** by an absorbent (soda lime or baralyme) (200 mL/min) to prevent rebreathing.

In the semi-closed system, CO₂ absorption is not needed.

- **Addition of anesthetic gases and vapors** (although minimal) to the system to replace those lost by tissue uptake. The main bulk of these anesthetics is recycled and re-breathed by the patient after CO₂ absorption.

Gas analyzers are recommended to ensure that the concentrations of O₂, CO₂, and anesthetic vapors are satisfactory.

Components:

- 1- A fresh gas flow (FGF) source.
- 2- Inspiratory and expiratory unidirectional valves.
- 3- Inspiratory and expiratory corrugated tubes.
- 4- A Y- piece connector.
- 5- An adjustable pressure limiting valve (APL) valve.
- 6- A reservoir bag.
- 7- A canister containing CO₂ absorbent (soda lime or baralyme).
- 8- A bag/ventilator switch.

Arrangement of the Components:

There are many arrangements but the following arrangement is preferred.

1- A Y-Piece Connector:

It is connected, so closely, to the patient's endotracheal tube to decrease the dead space (where the apparatus dead space is the common channel of the Y-piece only).

Unlike Mapleson circuits, the breathing-tube length does not affect the dead space due to presence of unidirectional flow in them.

2- Unidirectional Valves:

They should be relatively close to the patient, but not on the Y-piece, as this makes the circuit heavier when it is connected to the endotracheal tube intraoperatively.

3- The Fresh Gas (FG) Inlet:

It is placed between the canisters and the inspiratory valve.

If it is positioned downstream from the inspiratory valve, FG may bypass the patient during exhalation and become wasted.

If it is positioned between the expiratory valve and the canisters, FG may be diluted by re-circulating gas and the volatile anesthetics may be more absorbed or released by soda lime granules, thus slowing induction and emergence.

4- The Spill (APL) Valve:

It is placed immediately before the FG inlet and after the canister to minimize venting of FG.

It can be placed also before the canister, thus allowing the expired gas (containing CO₂) to be vented before reaching the canister, conserving the soda lime and decreasing its exhaustion.

5- The Canister and the Reservoir Bag:

They should be placed in the expiratory limb so that they do not increase the apparatus dead space even if the canisters are empty.

N.B.: The vaporizer position is either VIC or VOC (as discussed before).

Advantages of the Circle System

- 1- It is more economical because less anesthetic gases and vapor are used but this is balanced by the added cost of soda lime.
- 2- It increases the humidity of the inspired gases, thus reducing heat loss from the patient.
- 3- It decreases the risk of pollution of the operating room.

The Unidirectional Valves:

- They contain a **ceramic or mica disk** resting horizontally on an **annular valve seat**. They are mounted normally in a transparent glass dome so that they can be observed to be functioning correctly (figure 6-66).
- Forward flow displaces the disc upwards, allowing the gas to pass through the circuit. Reverse flow pushes the disc against its seat, preventing return of the gas.
- The expiratory valve (placed on the expiratory limb) is exposed to the humidity of alveolar gas, so it can be differentiated easily from the inspiratory valve.
- Valve incompetence is usually due to disc or seat irregularities. This can cause rebreathing of CO₂ resulting in hypercarbia.

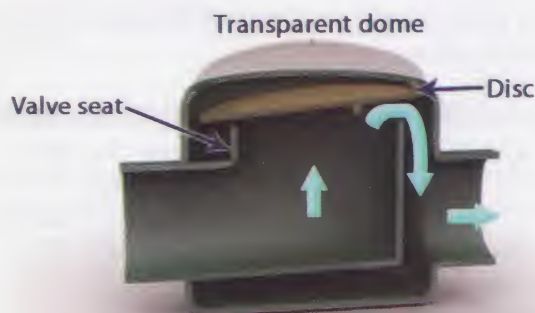


Figure 6-66: A unidirectional valve

The Canister (the Absorber)

The absorbent granules (soda lime, baralyme, or amsorb) are contained within one or two containers or canisters which fit snugly between a head and a base plate. They should have:

- **Transparent walls** to allow clear inspection of the color of the indicator dye.
- A **baffle system** to allow direction of flow and uniform dispersion of exhaled gases to minimize channelling.
- A **dust trap** at the bottom of the canister to collect alkaline dust and moisture.
- A **large size** canister can be used with less frequent changing of the exhausted soda lime because the canisters are not part of the apparatus dead space as they are present on the expiratory limb of the circuit.

Types of Granules:

	Soda Lime	Baralyme	Amsorb plus
Composition	1- Calcium hydroxide, 'Ca (OH) ₂ ' (94%); acts as the major hydroxide used to neutralize CO ₂ . 2- Sodium hydroxide 'Na OH' (5%) Potassium hydroxide 'K OH' (1%) Both act as activators. 3- Silica (0.2%); reacts with Ca (OH) ₂ to form calcium silicate which is very hard.	1- Calcium hydroxide, 'Ca (OH) ₂ ' (80%). 2- Barium hydroxide 'Ba (OH) ₂ ' (20%). Both act as the major hydroxide used to neutralize CO ₂ . There is no silica.	1- Calcium hydroxide, 'Ca (OH) ₂ ' (>80%) is the major hydroxide that neutralizes CO ₂ . 2- Calcium chloride, 'CaCl ₂ ' (small%) is added to decrease the risk of interaction with volatile agents as it acts as humectant and thereby allowing greater availability of water. Water content is 13-18%.
Method of hardness	Hardness of soda lime granules is produced by silica to prevent their powdering into alkaline dust. Formation of this alkaline dust must be prevented because it produces irritation of the patient's airway resulting in bronchospasm.	Hardness is produced by water of crystallization in the octahydrate salt of barium hydroxide.	Hardness is produced by calcium sulfate and polyvinyl pyrrolidone .
Mesh size	4-8	4-8	4-8
Indicator dye	Ethyl violet	Ethyl violet	Ethyl violet
Usage	It is more commonly used because: • Its absorptive capacity is 14-23 L CO₂/100 gram granules i.e., more efficient . • It is less expensive . • It produces a lesser degree of interaction with the volatile anesthetic agents .	It is less commonly used because: • Its absorptive capacity is 9-18 L CO₂/100 gram granules i.e., less efficient . • It is more expensive . • It produces a greater degree of interaction with the volatile anesthetic agents .	It is a newly introduced CO ₂ absorbent. It is safe to be used with volatile anesthetics (in contrast to soda lime and Baralyme) as it does not interact with volatile agents (i.e., no compound A or carbon monoxide production).

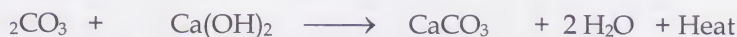
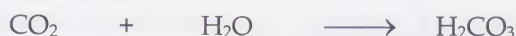
Neutralization Reaction:

Neutralization of CO_2 is done as a base neutralizing an acid. The base is the hydroxide and the acid is the carbonic acid. The following reactions occur:

a) With Soda Lime:

- At first, CO_2 (due to tissue metabolism) reacts with the **water** to form **carbonic acid**. Water is essential for the reaction (reaction A). The source of the water is:
 - soda lime (14-19%)
 - exhaled gases
 - the chemical reaction.
- Then, carbonic acid reacts with the hydroxides present in soda lime;
 - At first with **sodium and potassium hydroxide (fast reaction, B)**,
 - Then with calcium hydroxide (**slow reaction, C**).

The end results of the reactions are **carbonates, water, and heat** (i.e., an exothermic reaction).

**b) With Amsorb plus:**

The **water** formed by neutralization of CO_2 is useful in:

- Humidification of the inspired gases.
- Dissipating some of the heat generated by the exothermic neutralization reaction.

The **heat** of the reaction can be detected by the warmth of the canister containing the soda lime (the temperature in the center of a soda lime canister may exceed 60°C). Absence of this warmth indicates failure of the soda lime to neutralize CO_2 (figure 6-67).

Indicator Dyes:

- **Chemical pH-sensitive dyes** are added to the soda lime and the baralyme. When CO_2 is absorbed, the pH of the medium is changed; therefore, the color of the dye will change.
- **Ethyl violet** is the most common indicator dye used by manufacturers. Its color is changed **from white to violet** when soda lime or baralyme are exhausted.
- Although exhausted granules may revert to their original color if left (rested), they must not be reused because their absorptive capacity is not recovered. With amsorb plus, the color of indicator does not revert to its original color.



Figure 6-67: Amsorb plus

- Other indicator dyes rarely used:

	Color When Fresh	Color When Exhausted
Ethyl violet	White	Violet
Phenolphthalein	White	Pink
Clayton yellow	Red	Yellow
Ethyl orange	Orange	Yellow
Mimosa 2	Red	White

The Rate of CO₂ Absorbent Exhaustion

The rate at which soda lime becomes exhausted depends on:

- The capacity of the canister.
- The fresh gas flow rate.
- The rate of CO₂ production i.e., the rate of tissue metabolism.

Signs of exhaustion:

1- **Changes in color** of the absorbent granules, due to changes in the color of the indicator dye.

The absorbent should be replaced when 50-70% of the granules have changed in color (figure 6-68).

2- **Rise in end-tidal CO₂ by capnography.**

3- Clinical signs of CO₂ accumulation (**hypercapnia**) as tachycardia, hypertension, flushed skin, sweating, and increased wound oozing.

In a completely closed system, a standard 450-gram canister becomes inefficient after approximately 2 hours.

Recently, an anesthetic-gas monitor is applied to the anesthetic gases. If CO₂ is found in the inhaled gas, this is the time at which the soda lime must be changed.

Efficiency of CO₂ Absorption:

1- The Size of Absorbent Granules:

- The size of soda lime, baralyme, or amsorb granules is expressed as the **mesh size**.

The mesh size is **the number of openings per linear inch in a wire screen or sieve, through which the granules can pass** i.e., a 4 mesh sieve has 4 openings per inch (4 strands per linear inch), and 8 mesh sieve has 8 openings per linear inch.

- The optimal size of granules is from 4-8 mesh i.e., the diameter of the granules ranges from 1/4 to 1/8 inch because:
 - Larger sized granules are avoided as this decreases the surface area for CO₂ absorption.
 - Smaller sized granules are avoided because this increases the resistance to breathing.



Figure 6-68: Changing the color of soda lime from white (left) to violet (right)

2- The Volume of the Inter-Granular Space:

- To ensure complete CO₂ absorption, the air space between the granules (i.e., the inter-granular space) when the canister is tightly packed should be equal to or exceed the tidal volume of the patient. If the patient's tidal volume exceeds the inter-granular space, CO₂ accumulation will occur.
- The intergranular space is roughly equal to 50% of the canister's capacity.

3- Channelling:

- It is the easy passage of expired gases through areas of loosely packed granules (unfilled areas with granules). This will cause incomplete CO₂ absorption because most of the granules are bypassed.
- Channelling is decreased by:
 - Tight packing of the canister by absorbent granules.
 - Holding the absorbent granules in space by screens and baffles in the canister, to help direction of the flow and uniform dispersion of exhaled gases through the canister.
 - Mounting the canister vertically.

N.B.: Interactions of CO₂ absorbent with volatile anesthetics are discussed later.

Monitoring of Low-Flow and Closed Circuits

1- An **O₂ analyzer**: to measure inspired O₂ concentrations.

2- A **capnography**: to measure end-tidal CO_2 .

3- A **multi-gas analyzer**: to measure anesthetic agent concentration e.g., Raman spectroscopy.

Disadvantages (Problems) of Low-Flow and Closed Circuits:

A) Disadvantages of the Low Fresh Gas Flow (FGF):

1- FGF produces **unpredictable concentrations of O_2 and volatile anesthetics** to be inspired by the patient as follows:

- **Low FGF at the induction of anesthesia** (in the early period of administration within 10-15 minutes);

The system is filled with air (80% nitrogen) initially. If **low flow rates** of the anesthetic gases (preset by the anesthesiologists) are used, the anesthetic gases are **diluted by the air** (and nitrogen) in the circuit (due to their large volume) and lungs; therefore, **light anesthesia** may occur.

Even if the system is primed with a mixture of anesthetic gases at a low flow rate for the first 10-15 minutes, the initial rapid uptake of anesthetics by the patient results in a marked decrease in concentrations of anesthetic agents in the system, resulting in light anesthesia also.

Therefore, it is usually necessary to provide a **higher total fresh gas flow rate (e.g., 3-4 L/min) initially (for 15 minutes) at the beginning of the use** of the circuit to allow denitrogenation of the circuit and lungs. This high flow rate may be reduced subsequently by the anesthesiologist.

- **Low FGF during maintenance of anesthesia:**

If the FGF, coming from the fresh gas inlet, is low, it will be markedly affected by the exhaled gas coming from the canister. Therefore, the gas in the inspiratory limb (a mixture of the FGF and exhaled gas coming from the canister) will have very unpredictable concentrations of O_2 and anesthetics. Thus, if N_2O is used, the risk of hypoxia is very high with low FGF, unless an O_2 analyzer is used.

The higher the fresh gas flow rate, the less the effect of the gas, coming from the canister, on the anesthetic concentrations of the FGF; therefore, the patient will receive the same concentrations of O_2 and anesthetics present in FGF.

- Low FGF is **unable to produce rapid changes in the concentrations of inhaled anesthetic gases** i.e., slow changes in depth of anesthesia.

2- Low FGF produces **accumulation of foreign trace gases** within the circuit because they are not washed out by the low FGF. These gases include:

- methane from the intestine,
- acetone from the liver, in prolonged starvation or diabetes,
- ethanol in alcoholic patients,

and - carbon monoxide in heavy smokers.

Therefore, it is recommended to use intermittent periods of high FGF rates to washout these gases.

3- Low FGF **does not compensate for leaks** in the circuits.

4- Low FGF produces a greater degree of humidity than high flow rates.

Generally higher FGF rates: - speed induction and recovery,

- decrease the marked variations in the gas mixture,

- decrease the accumulation of foreign gases,

and - compensate for leaks in the circuit,

- but produce relatively lower degrees of humidity.

B) Disadvantages of a Circuit System:

1- It is **bulky and heavy**.

2- It is **more complex** than Mapleson systems; therefore,

- It is more liable to **disconnection and leakage**.

- **Malfunctioning of the unidirectional valves** e.g., if they stick in the open position may lead to **rebreathing** and if they stick in the closed position, total **occlusion** occurs.

N.B.: The disadvantages of the circle system (leaks, disconnection and malfunction of the unidirectional valves) can be detected by capnography.

3- There is a slight risk of **bacterial retention** in circle components that may lead to respiratory infections in subsequent patients. Therefore, it is better to have antibacterial filters incorporated in the circuits.

C) Disadvantages of CO_2 Absorbents:

(The Interaction between the CO_2 Absorbent and Inhalational Anesthetics)

The heat (60°C) and strong alkalinity of soda lime and baralyme can decompose volatile anesthetics producing toxic by-products. This is discussed in details in chapter "Pharmacology of anesthesia and intensive care".

Valves Associated with Anesthetic Machines and Breathing Systems

- 1- Pressure reducing valves.
- 2- The flow control valves of the flowmeter.
- 3- The emergency oxygen flush valve (oxygen bypass valve).
- 4- Ambu E valve.
- 5- Non-rebreathing valve and reservoir valve assembly of the resuscitation bags.
- 6- Adjustable pressure-limiting valve.
- 7- The unidirectional valve (expiratory and inspiratory).

All these valves are discussed in the previous chapters.

In addition to the following valves:

8- Fail-safe valve (O₂ failure safety valve):

This valve is designed to shut off or decrease the supply of N₂O when O₂ pressure falls below 20 psi. This prevents the delivery of a hypoxic gas mixture from the machine to the patient.

9- Pressure relief valve (safety valve):

This valve prevents damage of anesthetic machines especially flowmeters and vaporizers if the common gas outlet becomes obstructed. It is set to operate at 30-40 kPa (300-400 cmH₂O). It is situated at the end of the back bar, downstream from the vaporizer.

A similar valve is incorporated into ventilators. It is set to a lower level e.g., 7 kPa.

Properties of the Ideal Anesthetic Breathing System

None of the breathing systems fulfill all the properties of ideal breathing systems.

An ideal breathing system should be:

- Simple, easy to use, and light weighted.
- Adequate for O₂ and anesthetic gases supply in stable concentrations.
- Adequate for CO₂ and other foreign gases removal.
- With minimal resistance and minimal apparatus dead space.
- Easily switched from spontaneous to controlled ventilation and vice versa.
- With adequate scavenging system for waste gases, so less pollution to the operating room occurs.
- Economical for anesthetic gases.
- Without expensive components needed to be changed frequently e.g., soda lime.
- With easy and complete monitoring of the anesthetic gases and O₂.
- Able to conserve patient's heat and humidity.
- Easily sterilized or disposable to decrease cross infection.
- Used in all age groups.

Safety Features of Breathing Circuits

- **Breathing tubes** should be:
 - made of silicon (**autoclavable**) or plastic (**disposable**) to avoid cross-infection,
 - **corrugated** to avoid its closure during kinking,
 - **wide** (usually 22mm) to create a low-resistance pathway,
 - at least **equal to the patient's tidal volume**, to act as a reservoir for anesthetic gases,
 and - with suitable compliance.
- **Adjustable pressure-limiting valve (APL valve)** should be present to prevent damage of the patient's airway and lungs.
- **Reservoir bag (breathing bag)** should be present to act as:
 - a reservoir of anesthetic gases,
 - a method of generating positive pressure ventilation,
 and - have high compliance which generates a pressure rarely exceeds above 60 cm H₂O.
- A **bag/ventilator switch** should be present.
- The **canister (the absorber)** should have:
 - **Transparent walls** to allow clear inspection of the color of the indicator dye.
 - A **baffle system** to allow direction of flow and uniform dispersion of exhaled gases, to minimize channelling.
 - A **dust trap** at the bottom of the canister to collect alkaline dust and moisture.

- A **large sized** canister with less frequent changing of the exhausted soda lime, because the canisters are not part of the apparatus dead space, as they are present on the expiratory limb of the circuit.
- **Amsorb** is a newly introduced CO₂ absorbent. It is safe to be used with volatile anesthetics.
- **Monitors for low-flow and closed circuits** should be available as:
 - An **O₂ analyzer**: to measure inspired O₂ concentrations.
 - A **capnography**: to measure end-tidal CO₂.
 - A **multi-gas analyzer**: to measure anesthetic agent concentration e.g., Raman spectroscopy.
- **Pressure relief valve (Safety valve).**

N.B.: Safety features to prevent delivery of hypoxic gas mixture to the patient:

- 1- An oxygen analyzer to measure the inspired O₂ concentration (the most preferred).
- 2- An alarm device to give signals when O₂ supply fails.
- 3- Fail-safes valves to shut off or decrease the supply of N₂O.
- 4- A proportioning system to control a safe ratio of N₂O: O₂.

PART 6: MECHANICAL VENTILATORS

Before using any ventilator, it is essential to fully understand its functions; failure to do so may result in the delivery of a hypoxic gas mixture, rebreathing of CO₂, and/or delivery of a mixture that contains no anesthetic gases.

If an unfamiliar ventilator is encountered, it may be helpful to use a "dummy lung" (a small reservoir bag on the patient's connection) (figure 6-69) and details may be obtained from the manufacturer's user handbook or a specialist book.



Figure 6-69: A test dummy lung

Types of Mechanical Ventilation

Mechanical ventilation of the lung may be achieved by several mechanisms:

A) Negative Pressure Ventilation:

Idea: It does not require endotracheal intubation as negative pressure is applied to the abdomen and thorax to draw air into the lungs via the upper airway during inspiration. It is very rarely used.

Types: Negative pressure is either applied:

- 1- Around the **patient's whole body** except the head and neck e.g., Cabinet ventilator (tank respirator) or iron lung.
- 2- Around the **thorax and abdomen** only e.g., cuirass ventilators.

Disadvantages:

- It can not overcome a substantial increase in airway resistance or a decrease in pulmonary compliance.
- It causes pooling of venous blood in the abdomen causing **tank shock**.

B) Positive Pressure Ventilation:

Idea: They periodically create a pressure gradient between the machine circuit and alveoli allowing inspiratory gas flow, while exhalation occurs passively.

Types: Positive pressure is either applied:

- 1- Around the **thorax and abdomen** only e.g., inflatable cuirass ventilators.
- 2- To the **lung** through a tracheal tube or mask e.g., modern anesthesia and intensive care unit ventilators.

Classifications

Several classifications exist. Ventilators are classified according to:

- 1- Power source.
- 2- Ventilator circuit design.
- 3- Inspiratory phase characteristics.
- 4- The method of cycling from inspiration to expiration.
- 5- Expiratory phase characteristics.
- 6- The method of cycling from expiration to inspiration.

1- Power Source:

The power source required to operate a mechanical ventilator is either:

- a- **Pneumatic** (i.e., gas) which is either: - high pressure compressed gas,
or - Venturi effect.

- b- **Electrical**.

Modern electronic ventilators require **both** pneumatic and electrical power sources.

2- Ventilator Circuit Design:

There are two types of circuit design:

a- Single-Circuit System:

Idea:

- In **piston ventilators**, the bellows is driven by a piston (or a crank) electrically. It requires either minimal or no pneumatic (oxygen) power e.g., Rotary piston ventilator (figure 6-70).
- During volume-controlled ventilation, the piston moves at a constant velocity whereas during pressure-controlled ventilation, the piston moves with decreasing velocity.

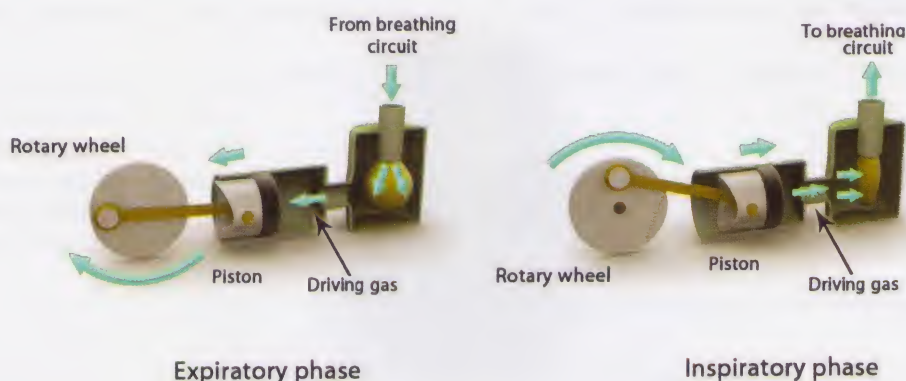


Figure 6-70: Rotary Piston ventilator

Advantages:

It is accurate in delivering tidal volumes to patients with very poor lung compliance and to very small patients.

b- Double-Circuit System: (more common in modern ventilators).

There are two distinct pneumatic circuits within the ventilator that are separated by the bellows' wall':

The external circuit:

- It contains the compressed gas (45-50 psi) which acts as **the driving force that compresses the bellows**. It is routed from the ventilator pneumatic power outlet and is present between the inside wall of the plastic enclosure and the outside wall of the bellows.
- Pressurization of gas in the external circuit compresses the pleated bellows inside, forcing the gas inside the bellows into the breathing circuit and to the patient.
- The driving gas is either **100% oxygen or a mixture of oxygen and air**. It is safer to have pure oxygen as the driving gas, because the fraction of inspired oxygen (F_{iO_2}) will be high if there is a leak in the bellows.
- **The amount of O_2 consumed** in the external circuit should be at least equal to minute ventilation.

Some anesthesiologists reduce O_2 consumption by incorporating a Venturi device that draws in room air to provide air/ O_2 pneumatic power.

- A **leak in the ventilator bellows** can transmit high gas pressure to the patient's airway, potentially resulting in pulmonary barotrauma, but the gas delivered to the patient will be enriched with O₂. This problem is detected by the O₂ analyzer, where a higher, than expected, rise in inspired O₂ concentration is detected. Some ventilators have a built-in drive gas regulator that reduces the drive pressure (e.g., to 25 psi) for added safety.
- A **free breathing valve** is incorporated in the circuit to allow outside air to enter the external circuit (i.e., the rigid chamber). This allows the bellows to collapse if the patient generates negative pressure by taking spontaneous breaths during mechanical ventilation.

The internal circuit:

- It contains the tidal volume (preset by the anesthesiologist) delivered to the patient from a **bellows**. It is an extension of the anesthetic breathing circuit i.e., it contains the anesthetic gas mixture (figure 6-71). The bellows takes the place of the reservoir bag in the anesthesia circuit.

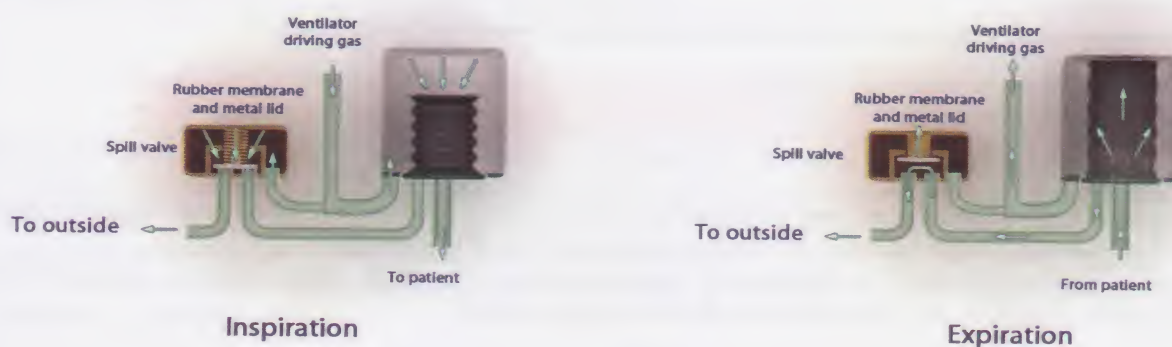


Figure 6-71: A double circuit pneumatic ventilator

- The tidal volume is determined by adjusting the level of the bellows.
- The bellows is formed from either a rubber or latex-free material situated in a clear rigid plastic enclosure.
- There are two types of bellows classified according to the direction of movement of the bellows during the expiratory phase:
 - a- **Ascending (standing) bellows:** ascends during the expiratory phase. It is used in **modern** ventilators.
 - b- **Descending (hanging) bellows:** descends during the expiratory phase. It is used in **old** ventilators.
- **The ascending bellows is safer** because an ascending bellows will not fill and thus will draw attention, if a total disconnection occurs.

On the other hand, a descending bellows will continue its upward and downward movements during a total disconnection due to the gravity, especially the weighted bellows, in spite of disconnection of the breathing circuit.

Additional Components in the Ventilator Circuits:

- **A bag/ventilator switch:**

It should be incorporated in the single- or double-circuit system.

When the switch is turned to "bag", the ventilator is excluded and spontaneous/manual (bag) ventilation is possible.

When it is turned to "ventilator", the breathing bag and the spill (APL) valve are excluded from the breathing circuit.

In some new anesthesia machines, the APL valve may be automatically excluded from the circuit when the ventilator is turned on.

• **Adjustable Pressure-Limiting Valve (APL Valve) or Spill Valve of the circuit:**

It must be incorporated in the breathing circuit (see before in "Anesthesia Breathing Systems").

• **Adjustable Pressure-Limiting Valve (APL Valve) or Spill Valve of the ventilator:**

This valve is incorporated in the anesthesia ventilator whether the single- or the double-circuit system.

During inspiration, the valve is pneumatically closed so that positive pressure can be generated.

During expiration, the pressurized gas is vented out and the ventilator spill valve is no longer closed; the ventilator bellows or piston refill during expiration and the spill valve opens as circle system pressure rises.

Sticking of the APL valve leads to abnormally elevated airway pressure during exhalation.

N.B.: The incorporation of a **humidifier and bacterial filters** in the ventilator circuits is essential.

3- Inspiratory Phase Characteristics:

Ventilators are classified according to the character of the inspiration into:

a- Constant Ventilators either:

• **Constant pressure generators:**

They produce pressures which are constant during the inspiratory phase, irrespective to the flow (and tidal volume) delivered to the patient i.e., **constant pressure but variable volume**.

They change from inspiration to expiration when a predetermined pressure is reached i.e., they are **pressure controlled ventilators** (see later).

• **Constant flow generators:**

They produce gas flow rates (and volumes) which are constant during the inspiratory phase irrespective to the pressure generated in the patient's lung and circuit i.e. **constant flow and volume but variable pressure**.

They change from inspiration to expiration when a predetermined volume is reached i.e., they are **volume controlled ventilators** (see later).

b- Non-Constant Ventilators either:

• Non-constant pressure generators.

• Non-constant flow generators.

They produce pressures or gas flow rates that vary during the cycle but remain constant from breath to breath.

An example of the non-constant flow generators is a rotary piston ventilator that generates a sinusoidal flow pattern i.e., like half a cycle of a sine wave.

4- The Method of Cycling from Inspiration to Expiration:

Termination of the inspiratory phase and beginning of the expiratory phase are triggered by one of the following:

a- Pressure-cycled or limited (controlled or targeted) ventilator.

b- Volume-cycled or limited (controlled or targeted) ventilator.

c- Time-cycled (Target) Ventilator.

They are discussed in the chapter of "Intensive (Critical) Care".

5- Expiratory Phase Characteristics:

Expiration is passive where the air in the lung is allowed to be exhaled to the outside and the airway pressure is decreased either:

a- To atmospheric pressure i.e., without positive end-expiratory pressure (without PEEP).

b- To a certain pressure level i.e., with positive end-expiratory pressure (with PEEP).

PEEP is produced by pressurization of the expiratory valve in the ventilator or any breathing apparatus, allowing exhalation only when airway pressure equals or exceeds the selected PEEP levels. This resistance to expiration is provided by a spring tension (as in spill valve), a water column, a weighted ball or a pressurized balloon or diaphragm.

6- The Method of Cycling from Expiration to Inspiration:

The change from expiration to the next inspiratory phase is achieved by either:

a- Time-cycled.

or b- Pressure-cycled.

The method of cycling (from expiration to inspiration and also from inspiration to expiration) and the ability to detect the effort of the patient by sensing the change of the pressure or the flow **determines the ventilator modes** e.g., controlled mode, synchronized intermittent mandatory ventilation (SIMV)...etc. More details about the modes of ventilation are discussed in chapter of "Intensive care".

Microprocessor-Controlled Ventilators:

These are **the most recent ventilators in anesthesia and intensive care.**

They contain a microprocessor (an electronic control box) that can deliver a wide range of tidal volumes, peak inspiratory pressures, respiratory rates, inspiratory flows, inspiratory plateau, inspiratory to expiratory ratios (I: E ratio), intermittent sighs, positive end-expiratory pressure (PEEP) and a variety of cycling mechanisms. These ventilators can also combine more than one mode.

These ventilators require compressed O₂ to power the bellows, and electricity to power the control box.

Minute Volume Divider Ventilators

(e.g., Manley Pulmovent Ventilator)

- This type of ventilator divides the total minute volume which is the fresh gas flow delivered from the anesthetic machine (e.g., 7 L/min). Therefore, the fresh gas flow should equal the minute volume. If the tidal volume is 0.5 L, the ventilator rate will be $7 \div 0.5 = 14$.

Therefore, the ventilator is sometimes referred to as a volume-cycled ventilator. Actually, although a near-constant pressure is generated, it is applied via a flow control, so that neither pressure nor flow is constant at the patient's airway (figure 6-72).

- A fresh gas flow of, for example, 7 L/min inflates a reservoir bellows. The gas in the bellows has a pressure of about 10-12 kPa due to the force exerted on the bellows by the springs. When the bellows are inflated to the preset volume, the cycling mechanism opens a valve to allow the bellows to inflate the patient's lung. The flow is controlled by a flow control valve.

There is also a safety valve at the patient's side to limit pressure to a maximum of 7 kPa.



Figure 6-72: A Manley pulmovent ventilator

Differences between Anesthesia Ventilators and Intensive Care Ventilators

	Anesthesia Machine Ventilators	Intensive Care Ventilators
Inspiratory flow	They can only provide low gas flow about 50 L/min.	They can provide higher gas flow rates up to 180 L/min.
Peak inspiratory pressure (PIP)	They can only generate PIP up to 50-60 cm H ₂ O; therefore, they cannot deliver gas flow against increased airway resistance.	They can generate PIP up to 120 cm H ₂ O; therefore, they can deliver gas flow against increased airway resistance.
Tidal volume	They deliver a limited range of tidal volumes.	They deliver a <i>wide range of tidal volumes</i> e.g., very low tidal volumes in pediatrics and protective lung strategy in acute respiratory distress syndrome.

Modes	Usually volume controlled mode only. Recently, some types incorporate synchronized intermittent mandatory ventilation (SIMV).	Many modes can be applied e.g., assisted controlled, SIMV, pressure support, inverse ratio, pressure controlled, and biphasic positive airway pressure ventilation (BiPAP).
PEEP	Not available, but some types can deliver	Available
Delivery of anesthetic gases	Available	Unavailable

Recently, many anesthetic machines incorporate a ventilator resembling intensive care ventilators. Also other intensive care ventilators may incorporate a vaporizer to provide anesthesia for e.g.,:

- Patients with acute respiratory distress syndrome undergoing incision and drainage of abscesses.
- Burned patients with severe bronchospasm undergoing excision of skin grafts.

Monitoring and Alarms during Mechanical Ventilation

Monitoring and alarms are an integral part of all modern anesthesia ventilators. They include:

1- **Clinical observation of the patient** (color and chest movements) is very important even when sophisticated monitors are used.

2- **Disconnect alarms:** should be passively activated. There are 3 types:

- Low peak inspiratory pressure: that is always built-in the ventilator.
- Low exhaled tidal volume.
- Low exhaled carbon dioxide.

A small leak or partial breathing-circuit disconnection may be detected by subtle decreases in PIP, exhaled tidal volume or end-tidal CO₂ before alarm thresholds are reached.

3- **Airway pressure measurement:** there are two measured airway pressures (peak inspiratory pressure or plateau pressure).

4- **Measurement of inspired O₂ concentration by an O₂ analyzer.**

5- **Measurements of inspired and expired tidal volumes by a spirometer.**

6- **Measurement of end-tidal CO₂ by a capnography.**

7- **Measurement of O₂ supply pressure:** if it is low, a characteristic visual and audible alarm should be present.

In addition to the monitors of the patient as:

- **Pulse oximetry.**
- **Hemodynamic monitors.**

More details about monitoring during mechanical ventilation are discussed in the chapter of "Intensive (Critical) Care".

Problems Associated with Ventilators

1- Breathing Circuit Problems:

a- **Breathing circuit disconnection:**

It is the **major cause of catastrophic anesthetic accidents**. The most common disconnection site is the Y-piece of the circle system.

Plastic connections may distort during autoclaving, and even metal ones can be damaged by misuse, so regular inspection is recommended with replacement if needed.

Some breathing circuits have couplings with screw collars to prevent unintentional disconnections. However, the final connection at the patient is normally a simple cone fitting to allow rapid change of this coupling if needed.

b- **Breathing circuit leaks:** e.g., failure of the APL valve to close during the inspiratory phase.

Therefore in modern ventilators, presence of a bag/ventilator switch is essential to minimize this problem.

Detection of disconnection or leaks is done by:

- Auscultation of breath sounds.
- Observation of chest wall excursions.
- Observation of the filling of ascending bellows.
- Pneumatic and electronic pressure (visible or audible) alarm monitors.
- Monitoring of exhaled tidal volume and minute volume.
- Capnography where there is a decreased or absent end-tidal CO₂ concentration.

c- **Breathing circuit compliance:** as above.

2- Bellows Assembly Problems:

The main problem is the presence of a leak (see above).

3- Control Assembly Problems:

It is either electrical failure or mechanical failure.

4- Ventilator's APL Valve Problems:

a- Sticking of the valve: results in abnormally elevated airway pressure during exhalation that may cause barotrauma to the patient.

b- Incompetence of the valve: results in abnormally low (inadequate) airway pressure during inspiration that may cause hypoventilation to the patient.

Safety Features of Modern Anesthesia Ventilators

1- The ascending bellows is safer than the descending one because disconnection can be readily detected.

2- Pure O₂ is safer than a mixture of O₂ and air as a driving gas because in case of presence of a leak, enriched O₂ gas is delivered to the patient.

3- A bag/ventilator switch is important as it avoids the problems of APL valve.

4- Presence of alarms as above.

Indications, weaning, and complications of mechanical ventilation are out of concept of this chapter and should be revised in chapter "Intensive care".

PART 7: SCAVENGING SYSTEMS**Methods of Reducing Operating Theatre Pollution**

1- Usage of a scavenging system: It collects and removes waste anesthetic gases from the operating room to be vented to the outside.

2- Reduced use of anesthetic gases and vapors e.g., using of closed circle system with low flow, total intravenous anesthesia, or regional and local anesthesia.

3- Air conditioning units to allow rapid change of air. Efficient theater ventilation is essential. **15 air changes per hour** are recommended.

4- Care in filling of vaporizers: The use of agent specific connections reduces the risk of spillage.

Sources of Operating Theater Pollution

1- Exhaled gas from the APL valve.

2- Exhaled gas from the ventilator.

3- Leaks from equipment e.g., from an ill-fitting facemask.

4- During induction and emergence from anesthesia when the scavenging system is not applied.

5- Spillage during filling of vaporizers.

Risks of Chronic Exposure to Trace Quantities of Anesthetic Agents in Operating Theaters

1- Female anesthesia personnel who work in the operating room may be at a slightly increased risk of **spontaneous abortion** and of having an offspring with **congenital abnormalities**.

2- Female anesthesia personnel may be at a slightly increased risk of **cancer**.

3- Both male and female anesthesia personnel may be at a higher risk of **hepatic disease** as serum hepatitis which is not completely explained.

4- Female operation room personnel may be at an increased risk of **renal disease**.

5- Dentists and dental assistants may be at increased risk of **neurological disease** from exposure to N₂O.

• None of these conclusions have been definitively proved and laboratory studies have failed to link trace concentrations of modern anesthetic agents to mutagenic, carcinogenic, or teratogenic consequences in animal models.

• **The recommended upper limits of traces in the operating room for:**

N₂O is 25 ppm (part per million)

Halogenated agents (without N₂O) is 2 ppm.

Halogenated agents (with N₂O) is 0.5 ppm.

Scavenging System Components

It consists of 5 parts (figure 6-73):

- Gas collection assembly.
- Gas transfer tubing system.
- Receiving system (scavenging interface).
- Gas disposal tubing system.
- Gas disposal system.

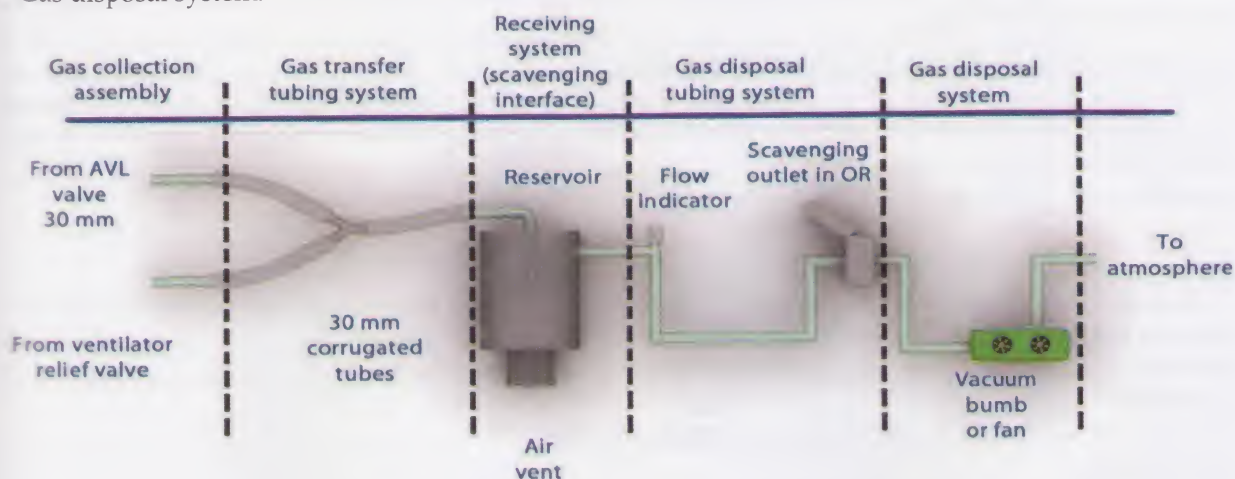


Figure 6-73: Scavenging system components

1- Gas Collection Assembly

It collects waste anesthetic gases vented from:

- The APL valve of the breathing system through a scavenging attachment with a diameter of 30 mm to avoid misconnection (figure 6-74).



Figure 6-74: A scavenging attachment

- The relief valve of the ventilator. The exhaust of the ventilator valve is also 30 mm in diameter.
- Occasionally, a funnel which is positioned near the expiratory valve, mask, the end of the T-piece, or the mouth of the patient to collect the expired gases (figure 6-75).



Figure 6-75: A funnel collecting the waste gases

2- Gas Transfer Tubing System

It carries waste anesthetic gases from the gas collection assembly to the receiving system.

The transfer tubing should be wide-bore (30 mm in diameter).

N.B.: All connections of the scavenging system should be **30 mm in diameter** to avoid misconnection and to decrease the resistance against expiration of the patient.

The anesthetic gas connections are 15 and 22 mm in diameters.

Moreover, scavenging system tubing should have a **color code of yellow** bands to distinguish them from the breathing system tubing.

3- Receiving System (Scavenging Interface)

It is the most important part of the scavenging system. It acts as a **pressure-balancing device** to protect the breathing system and the ventilator from excessive positive or excessive negative pressure changes within the scavenging system.

It is either open or closed.

a) An Open Interface (an Open Technique):

Idea:

- It consists of an **open-ended reservoir** (usually a cylinder) that is freely connected to the atmosphere to improve the efficiency i.e., there is **no valve** in this technique. This air break prevents any risk of obstruction and allows both positive and negative pressure to be relieved without a detrimental effect on the patient.

- It should be **used with an active vacuum disposal system**.

Disadvantages:

1- It is **less effective** than other systems.

2- It **needs an active vacuum** disposal system, with a high scavenging flow, typically 80 L/min to remove all expired gases.

b) A Closed Interface:

Idea:

- It communicates with the atmosphere through positive and negative pressure **relief valves**. The valves protect the patient from the excessive negative pressure of the vacuum system and excessive positive pressure from an obstruction in the disposal tubing.

- It can be **used with either active or passive disposal system**.

4- Gas Disposal Tubing System

It conducts waste anesthetic gases from the interface to the gas disposal system.

5- Gas Disposal System

It constitutes the final stage in which the anesthetic gases are transferred to the outside atmosphere.

It is either:

a) An Active Disposal System:

Idea:

- It withdraws waste gases to the outside by one of the following ways:

- A **vacuum**: It generates a negative pressure in the scavenging system.

- A **fan**: although the fan generates less vacuum but there will be no risk of pulmonary edema that may occur with the vacuum if applied via the breathing system directly to the patient's lungs.

- An **injector (a Venturi system)**: It is powered by compressed air or O₂ (but may increase the risk of fire) (figure 6-76).

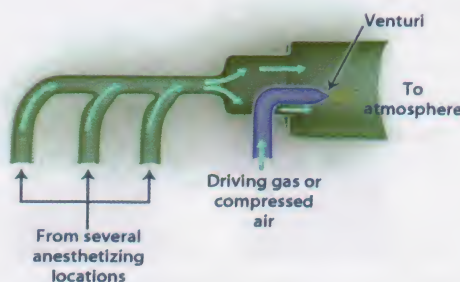


Figure 6-76: An injector active disposal system

The exhaust should be capable of accommodating 75 L/min continuous flow with a peak flow of 130 L/min.

It can be used **with an open or closed interface**. The one used with the open interface does not contain any valve but the one used with the closed interface should have the following components (figure 6-77):

1- A **positive pressure relief valve**: to vent excess waste gases to the atmosphere if the system pressure exceeds + 5 cm H₂O.

2- A **negative pressure relief valve**: to entrain room air if the system pressure is more negative than - 0.5 cm H₂O.

3- A **5-L reservoir bag**: to store excess waste gas until it is eliminated by the vacuum system

The system is tested according to the British standard as follows; the pressure at the exhaust port must not exceed 50 Pa (0.5 cm H₂O) when tested with a flow of 30 L/min into the system.

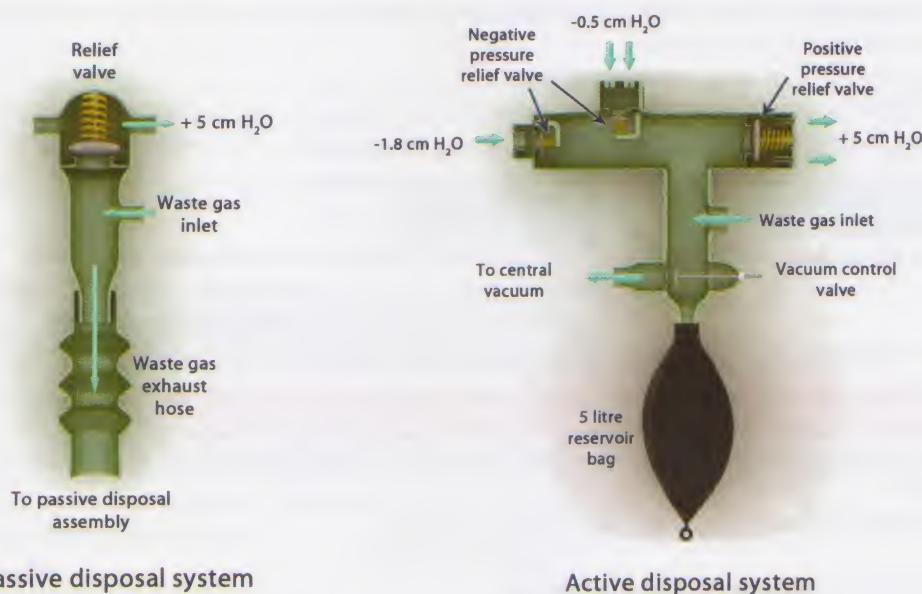


Figure 6-77: A closed scavenging interface

b) Passive Disposal System:

Idea:

It uses the pressure of the waste gas itself generated by the patient during expiration to help waste gas elimination. It conducts the waste gas through wide-bore tubes to avoid the occurrence of high resistance against patient's expiration (figure 6-78).

It is used **with closed interface only** and contains a **positive pressure relief valve only**. The valve opens at a preset level of + 5 cm H₂O if an obstruction occurs in the disposal system.

The presence of the **reservoir bag** is an **option** as some systems contain it and others do not.

There is no negative pressure relief valve, injector, fan, or vacuum.

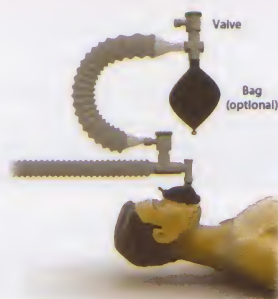


Figure 6-78: Passive disposal system

Disadvantages:

Excessive positive or negative sub-atmospheric pressure may be caused by wind movements at the outlet that may affect the exhaust of the waste gas. Therefore, to avoid this problem, the expired gases can be conducted to the exit grille used for the theater ventilation.

N.B.:

- **Excessive positive pressure** due to obstruction or occlusion of the scavenging pathways can be transmitted to the breathing system leading to **barotraumas**. This can be balanced by the **positive pressure relief valve**. This valve is mandatory **in both active and passive disposal systems**.
- **Excessive negative pressure** in the scavenging system due to high vacuum flow rate can be transmitted to the breathing system and is manifested as collapse of the reservoir bag. This can be balanced by the **negative pressure relief valve**. This valve is mandatory **in the active disposal system only**.

c) Assisted Passive (Semi-Active) Disposal System:

Idea:

It uses the non-recirculating air conditioning system of the operating room for elimination of waste gases where the gas disposal tubing is connected to the exit grille of the non-recirculating air conditioning system. The flow generated in the air conditioning system generates a low negative pressure to vent the waste gas to the outside atmosphere.

Disadvantage:

It has a **variable performance and efficiency**. The exit flow of the theater ventilation (air conditioning) should be of a suitable flow value and should not re-circulate. Therefore, the use of an exit grille is **inappropriate** if the theater ventilation is designed to re-circulate the flow or if the flow is variable.

Safety Features of Scavenging Systems

- 1- An active disposal system (vacuum system) should have:
 - A positive pressure relief valve.
 - A negative pressure relief valve.
 - A 5-liter reservoir bag.
- 2- A passive disposal system should have:
 - A positive pressure relief valve.

Safety Features of Modern Anesthetic Machines

Every part of the modern anesthetic machines has safety features to provide safety to the patients. They include:

- 1- Safety features of **medical gas supply**:
 - Gas cylinders.
 - Pipeline supply.
- 2- Safety features of **pressure reducing devices**.
- 3- Safety features of **flowmeters**.
 - Safety features of **O₂ flush valves**.
 - Safety features of **O₂ supply (O₂ supply failure devices)**.
- 4- Safety features of **vaporizers**.
- 5- Safety features of **breathing systems**.
- 6- Safety features of anesthetic machine **ventilators**.
- 7- Safety features of **scavenging systems**.

In addition to the **safety features of monitors** that are used during anesthesia and intensive care. Safety features of each part are discussed in their corresponding chapters.

N.B.: Absence of safety features of anesthetic machine determines **anesthesia machine obsolescence**.

Safety Precautions (Checklist) of Modern Anesthetic Machines

They are the **routine procedures done by the anesthesiologists** to check and test the machine before its use to **ensure safety**.

N.B.: The difference between safety features and safety precautions, for example, the presence of an alarm system is a safety feature where as the checking and setting of the alarm limits are safety precautions.

A) Safety Precautions of High Pressure System

- Tests of the oxygen cylinders.
- Tests of the Piped Medical Gas Supply..... See before in "Medical Gas Supply".

B) Safety Precautions of Low Pressure System

1- **Flowmeters**: should be checked for:

- free movement of the bobbins throughout its range.
- absence of leaks or damaged flowmeter tubes.
- the operation of the emergency oxygen bypass control.

2- Vaporizers: should be checked for:

- filling level (adequate and not overfilled).
- tightening of vaporizers filler caps.
- fixing of vaporizers on the selectatec mounting system.
- leaking with vaporizer on and off by temporarily occluding the common gas outlet.

3- Anesthetic Breathing Systems: should be checked for:

- correct attachment of all hoses and reservoir bag.
- securing of all connections by "push and twist".
- well functioning of the unidirectional valves.
- unexhausted CO₂ absorbent.
- well functioning of the APL valve.
- a pressure leak test; the test should be performed on the breathing system by occluding the patient's port and compressing the reservoir bag.

4- Ventilators: should be checked for: - their well functioning and power supply.

- proper connections.
- setting the controls for use and ensuring that an adequate pressure is generated during the inspiratory phase.
- the proper function of pressure relief valve.
- the proper function of disconnection alarm.

5- Scavenging System: should be checked for: - proper functioning.**C) Safety Precautions of Emergency Equipment**

Emergency equipment should be easily available to the anesthesiologists. They include:

1- **A self-inflating resuscitation bag** appropriate for patient size (adult vs. pediatric) should be present and tested. This is **the most important equipment** according to Food and Drug Administration (FDA).

2- **Emergency airway management equipment**, stored in a difficult airway cart, should be available, such as emergency cricothyrotomy (catheter and injector as Sanders injector).

3- Other emergency equipment such as:

- a working flashlight.
- an suction apparatus.
- a backup battery for any electricity-dependent workstation.
- an O₂ tank and regulator.
- a malignant hyperthermia cart.
- a defibrillator.
- a fire extinguisher and knowledge of appropriate response to a fire, and an evacuation plan.

4- **The trolley, operating table, or bed** should have the ability to tilt the patient's head down.

Beside; resuscitation drugs should be available.

These precautions are beside **the precautions of the monitors.**

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- <http://www.simanest.org/>
- <http://www.asevet.com/resources/index.htm>
- <http://www.anesthesiatools.com/>

MONITORING DURING ANESTHESIA & INTENSIVE CARE

7

Part 1: Monitoring of the cardiovascular system

- Peripheral pulse
- Tissue perfusion and clinical assessment
- Electrocardiography (ECG)
- Arterial blood pressure: non-invasive and invasive
- Central venous catheterization
- Pulmonary artery catheterization
- Measurement of cardiac output (CO)
- Trans-esophageal echocardiography (TEE)
- Measurement of regional blood flow
- Measurement of blood loss

Part 2: Monitoring of the respiratory system

- Clinical monitoring
- Monitoring and alarms during mechanical ventilation
- Precordial and esophageal stethoscope
- Spirometry.
- O₂ monitoring
- CO₂ monitoring
- Anesthetic gas analysis
- Pulmonary function tests

Part 3: Monitoring of the nervous system

- Clinical monitoring
- Electroencephalography (EEG)
- Evoked potentials
- Cranial nerve monitoring
- Cerebral blood flow measurement
- Monitoring of cerebral oxygenation
- Monitoring of the intracranial pressure
- Monitoring of depth of anesthesia
- Neuromuscular monitoring

Part 4: Monitoring of the metabolism

- Temperature monitoring
- Tissue oxygenation monitoring
- Indirect calorimetry and Harris Benedict equation
- Monitoring of blood gases and acid base status
- Monitoring of fluid and electrolyte status
- Monitoring of hormonal status

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Monitoring devices are designed to monitor the function of anesthetic machines and the different systems of the patient. The word "monitor" derives from the latin "monero" i.e., to warn. A monitor means the continuous measurement of patient and anesthetic machine variables over time.

A) Monitoring of Anesthetic Machine Function and Other Devices includes:

1- Monitoring the Fresh Gas Supply:

- O₂ concentration analyzers to detect hypoxic gas mixture.
- Vapor concentration analyzers to avoid awareness of the patient.

2- Monitoring the Breathing System:

- O₂ concentration analyzers to detect inadequate fresh gas flow, valve malfunction, or disconnection of the inner tubes in Bain circuits
- CO₂ concentration analyzers to detect valve malfunction, rebreathing, or exhausted soda lime.
- Expired volume measurements during controlled ventilation to detect leaks or ventilator malfunction.
- Airway pressure monitoring.

3- Monitoring the Mechanical Ventilation.

4- Monitoring of Other Therapeutic Devices:

- Temperature monitoring of humidifiers.
- Temperature monitoring of blood warmers to avoid hemolysis if the temperature of blood exceeds 42°C.
- Excessive pressure alarm when obstruction occurs against infusion pumps.

B) Patient Monitoring

All systems of the patient should be monitored during anesthesia and intensive care admission:

1- Monitoring of the Cardiovascular System & Hemodynamic Status.

2- Monitoring of the Respiratory System.

3- Monitoring of the Nervous System.

4- Monitoring of the Metabolism.

5- Monitoring of Obstetrics.

Recommendations:

1- A **qualified anesthesiologist** must be present throughout the conduct of general anesthesia, regional anesthesia and monitored anesthesia care (**standard I**), to provide clinical observation of the patient and functional observation of the anesthetic machine. Presence of an anesthesiologist is **the most important monitor**. The anesthesiologist should make observations of the patient's mucosa, pupil size, response to surgical stimuli and movements of chest wall and reservoir bag. The ventilator and the gas flow should also be observed. The pulse should be palpated regularly and the lungs auscultated and where appropriate, urine output and blood loss should be measured. **A stethoscope must always be available.**

N.B.: Monitored Anesthesia Care (MAC):

It refers to monitoring the patient by an anesthesiologist during a procedure performed with intravenous sedation or local anesthesia administered by the surgeon.

It was previously referred to as local standby anesthesia.

During intensive care stay, an intensivist or intensive care specialist should be available.

2- Essential monitoring for all anesthetized and intensive care admitted cases includes (**standard II**):

- Electrocardiogram (ECG).
- Non-invasive blood pressure.
- Pulse oximetry.
- End-tidal CO₂.

In addition to:

- Neuromuscular monitoring.
- Body temperature.
- Gas analysis.

These are the essential monitors in all operative rooms in most countries. Other **more sophisticated monitors** such as, invasive arterial pressure monitoring, pulmonary artery catheterization, cardiac output, blood gas analysis, detailed ventilatory parameters...etc are used **according to the patient's condition and the judgment of the responsible anesthesiologist.**

3- Monitoring should be **started before induction and continued** until the patient recovers and during patient transfer (if required).

4- Monitoring is done **for general, local or regional** anesthesia, and monitored anesthesia care whatever the length of anesthesia is.

5- Monitoring **equipments** must be **checked** by anesthesiologists before usage by a checklist.

• As the routine preoperative evaluation of the patient is important, the routine preoperative checkout of equipment is also important.

• As close intraoperative observation of the patient is important, close intraoperative observation of the equipment is also important.

Figure 7-1 shows an anesthesia monitor.



Figure 7-1: An anesthesia monitor

PART 1: MONITORING OF THE CARDIOVASCULAR SYSTEM

includes:

- 1- Peripheral pulse.
- 2 - Tissue perfusion and clinical assessment.
- 3- Electrocardiography (ECG).
- 4- Arterial blood pressure: non-invasive & invasive.
- 5- Central venous catheterization.
- 6- Pulmonary artery catheterization.
- 7- Measurement of cardiac output (CO).
- 8- Trans-esophageal echocardiography (TEE).
- 9- Measurement of regional blood flow.
- 10- Measurement of blood loss.

I - Peripheral Pulse

Peripheral pulse can be detected by one of the following methods:

1- Regular Palpation.

2-Pulse Plethysmography:

Idea: It is based on **photo-plethysmography**. The skin of a suitable digit or of the ear pinna is illuminated by a weak source of light. The intensity of the light transmitted through or reflected by the digit waxes and wanes with each capillary pulsation detected by a photoelectric cell. The signal is transduced to be displayed as a waveform on an oscilloscope (figure 7-2).

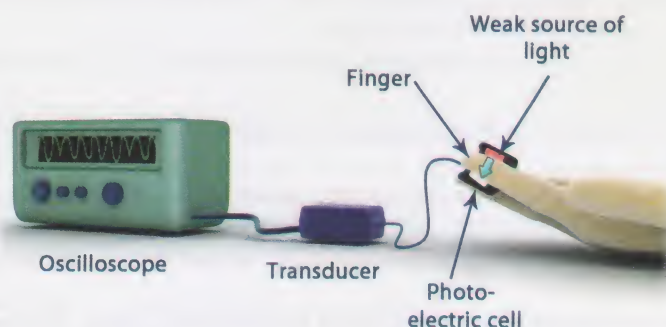


Figure 7-2: Pulse plethysmography

Value: It gives an idea about the pulse pressure as:

- High signal waves (similar to the arterial pressure waveform) indicate high pulse pressure e.g., peripheral vasodilatation or high cardiac output.
- Low signal waves (damped waveform) indicate low pulse pressure e.g., peripheral vasoconstriction or low cardiac output.

3- Penaz Technique. See later.

4- Pulse Oximeter. See later.

II- Tissue Perfusion and Clinical Assessment

It is the best clinical assessment for cardiac function and management of shock. It should be employed before more invasive techniques are done.

1- Peripheral Perfusion (by Skin):

a- Capillary Refill:

Rapid return of blood within 5 seconds to the nail bed after slight pressure indicates good peripheral perfusion.

b- Observation of Patient's Extremities (Especially in Children):

Warm, dry, and pink skin indicates adequate peripheral perfusion.

Cold and white skin indicates inadequate peripheral perfusion.

6- The Core-Peripheral Temperature Gradient:

One temperature probe is placed centrally e.g., in nasopharynx and the other temperature probe is placed peripherally e.g., on great toe.

Normally, the difference between them = $< 5^{\circ}\text{C}$

But • Decreased temperature gradient occurs in peripheral vasodilatation or high cardiac output states.

• Increased temperature gradient occurs in peripheral vasoconstriction or low cardiac output states.

4- Venous Occlusion Plethysmography:

It is not used routinely (as above).

2- Cerebral Perfusion:

Is performed e.g., by assessing the mental status.

3- Gastric Intra-mucosal pH (pHi):

The adequacy of gut mucosal perfusion is assessed indirectly by its pH.

If pHi is < 7.2 , it indicates mucosal ischemia.....see later.

4-Acid-Base Status and Serum Lactate:

Tissue hypoperfusion causes: • Decreased PaO_2 • Decreased pH (acidosis) • Increased s. lactate.

N.B.: Normal serum lactate is $< 2 \text{ mmol/L}$.

- In distressed patients, it is $2-4 \text{ mmol/L}$.

- In ischemic tissues, it is $> 4 \text{ mmol/L}$.

Other conditions that increase serum lactate are: • Thiamine deficiency.

• Bacterial pneumonia.

• Generalized trauma.

• Respiratory alkalosis.

• Generalized fits.

5- Mixed Venous O_2 Saturation ($\text{S}\bar{\text{v}}\text{O}_2$) or Tension ($\text{P}\bar{\text{v}}\text{O}_2$):

Normally, $\text{S}\bar{\text{v}}\text{O}_2$ is 75 % and $\text{P}\bar{\text{v}}\text{O}_2$ is 40 mmHg. If $\text{P}\bar{\text{v}}\text{O}_2$ is $< 28 \text{ mm Hg}$, it indicates poor tissue perfusion.

It should be interpreted with care as the presence of an arterio-venous shunt, may elevate the values despite tissue hypoxia.

6- Urine Output (UOP) for Renal Perfusion:**Indications:**

1- Congestive heart failure or shock.

2- Renal failure.

3- Hepatic failure.

4- During surgeries with large fluid shifts as in cardiac surgeries, major vascular or abdominal surgeries, surgeries in a jaundiced patient, lengthy surgeries as craniotomy, and when intraoperative diuretics are administered.

Value: It indicates renal perfusion which reflects: renal function, cardiovascular status, and fluid volume status. Normal UOP = $0.5 - 1 \text{ ml/kg/hour}$. Oliguria occurs when UOP is $< 0.5 \text{ ml/kg/hour}$.

7- Peripheral Pulse.**8- Arterial O_2 Saturation.****9- Arterial Blood Pressure.****10- Cardiac Output Measurement.**

They can give an idea about tissue perfusion.

III- Electrocardiography (ECG)

It indicates only **biological electrical potentials** generated by muscle cells, but **does not indicate cardiac output** as patients with very low cardiac output may have good ECG tracing. Therefore, ECG monitoring must be accompanied by tissue perfusion monitoring and peripheral pulse monitoring.

Potentials from the heart are transmitted through the tissues to the skin where they are attenuated; therefore, the size of the ECG signal detected is only 1-2 mV instead of the original action potential of about 90 mV of the cardiac cells.

Uses: It is used for the detection of:

1- **Arrhythmias:** by lead II: It is the most sensitive for arrhythmias.

2- **Myocardial ischemia:**

• By interpreting ST segment changes as:

- Flat or down-sloping ST segment depression exceeding 1 mm, 60 or 80 milliseconds after the J point (the end of QRS), especially with T wave inversion.

- ST segment elevation and peaked T wave.
- Recently, new automated ST segment analysis is available.

3- Conduction abnormalities.

4- Pacemaker malfunctions.

Choice of ECG Leads:

For maximum diagnostic information, it is necessary to use a 12-lead ECG, but it is too cumbersome for the operating room or intensive care environment. Therefore, 3- or 5-lead ECG is commonly used.

a) Three-Lead System:

Bipolar Lead System	Electrode Placement	Selected Lead on Monitor	Simulated ECG Lead	Advantages (best for...)
I	- RA at right arm - LA at left arm - LL, ground	I	I	- Lateral ischemia
II	- RA at right clavicle - LA, ground. - LL at left leg	II	II	- Arrhythmia - Inferior wall ischemia
III	- RA, ground - LA at left arm - LL at left leg	III	III	- Inferior ischemia
CM5 (Modified lead V5) (figure 7-3)	- RA over manubrium sterni - LA at apex (V5) (left 5 th intercostal space at anterior axillary line) - LL, ground	I	V5	- Anterior wall ischemia (precordial ischemia) - Arrhythmias
MCL1 (Modified central lead)	- RA, ground - LA at left clavicle - LL at V1 position	III	V1	- Arrhythmia - Conduction defect
CS 5 (central subclavian)	- RA at right clavicle - LA at apex (V5 position) - LL, ground	I	V5	- Anterior wall ischemia (precordial ischemia)
CB 5 (central back)	- RA over right scapula - LA at apex (V5 position) - LL, ground	I	V5	- Anterior wall ischemia (precordial ischemia). It is usually for thoracic surgery.
CC5	- RA at right axillary line - LA at apex (V5 position) - LL, ground	I		- Global ischemia.

RA = right arm lead i.e., negative (red),

LA = left arm lead i.e., positive (yellow),

LL = left leg lead i.e., indifferent (black) ground lead which is placed at any convenient site.

b) True lead V5: It is done by 5-lead ECG.

It is the best for detection of **anterior and lateral wall ischemia (i.e., left ventricle)**.

c) **Esophageal lead:** It is done by a special lead inserted inside the esophagus. It gives a clear ECG signal of the P waves because it lies close behind the atria of the heart.

It is the best for detection of **posterior wall infarction and arrhythmia** (it is better than lead II, but it is not commonly used in the operation room).

d) Intracavitary ECG electrode: It is rarely used.

Therefore, if only a single-channel monitor is available, the choice between leads depends on the prior history of a site of infarction. Because V5 is the most common site of ischemia in most patients (80% of ischemia); therefore, CM5-Lead I configuration is displayed (figure 7-3), but if a 2-channel monitor is used, both Lead II and V5 are displayed because they are the most common leads showing ischemia and arrhythmia.

After arrangement of leads, standardize ECG at 1 mV signals i.e., 10 mm deflection.

Print a preoperative trace to compare later on.

ECG Electrodes are either:

- a- **Silver chloride electrodes** (figure 7-4): It is better to clean the site of application by alcohol or degreasing agent to decrease skin's electrical resistance and increase the strength of the signals. Placing electrodes over bony prominences reduces noise from muscle contractions.
- b- **Needle electrodes**: in extensively burned patient.

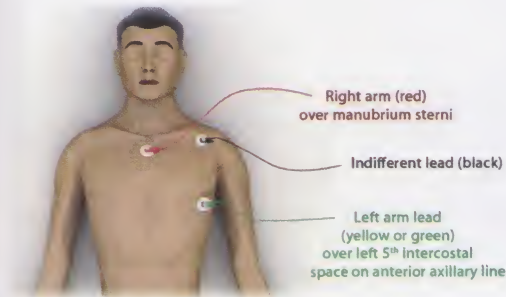


Figure 7-3: CM5-Lead I configuration

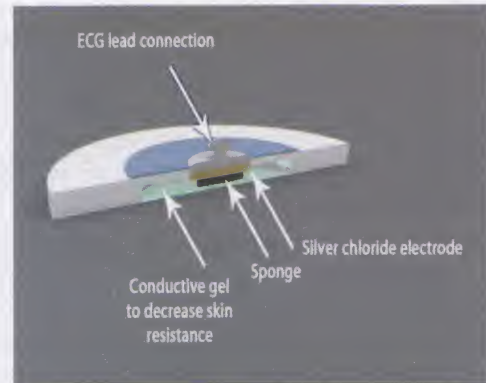


Figure 7-4: An ECG electrode with its cross-section image

Audible Beep should be set loud to warn both:

- The anesthesiologist: when his visual attention is directed to other responsibilities.
- The surgeon: in operations affecting the heart rate e.g., eye traction, and anal dilatation in order to stop the maneuver if bradycardia occurs.

N.B.: ECG is one of the following:

- 1- Three- lead ECG monitor.
- 2- Five- lead ECG monitor.
- 3- Twelve- lead ECG trace.
- 4- Holter or ambulatory ECG trace.
- 5- Exercise ECG trace.

N.B.: Interpretation of ECG trace is discussed in the end of this book.

N.B.: Biological Electrical Potentials

Definition and Origin:

- The membrane of a cell is composed of phospholipids and has a sandwich structure, with a hydrophobic fatty interior and a protein-carbohydrate exterior. The Na-K pump pushes sodium ions out of the cell, and potassium ions in through the cell membrane. These ions carry electric charges, so that the net result is a positive charge of around 90 mV at the exterior compared with the interior of the cell.
- During depolarization, sodium ions (and calcium ions in cardiac cells) move into the cell and potassium ions move out through the membrane. Finally, the membrane recovers its potential as the sodium-potassium pump restores the resting status.
- Adjacent areas of membrane are destabilized by the region of depolarization and undergo the same changes, so that a wave of depolarization spreads over the muscle. Similar changes occur at the surface membrane of a neuron to propagate the nerve impulse.
- These waves of electric potential changes are transmitted through the tissues overlying the nerves and muscles and can be detected by suitable electrodes placed on the skin and displayed.

Examples:

- a) Biological electrical potentials directly recorded:
 - Electrocardiogram (ECG).
 - Electroencephalogram (EEG).
 - Electromyogram (EMG).
- b) Evoked biological electrical potentials:
 - Somatosensory evoked potentials (SSEP).
 - Auditory evoked potentials.

IV- Arterial Blood Pressure (ABP)

Introduction:

- **Systolic blood pressure** arises from the force of contraction of the myocardium acting on the blood inside the heart. Assuming the heart as a sphere, **Laplace's law** for a sphere can be applied as follows:

$$P = \frac{2T}{R}$$

Where P = the pressure T = the tension in the ventricular wall R = the radius of the heart

Therefore, according to Laplace's law, a distended failing heart with a larger radius than normal will result in a decrease in the pressure produced.

Diastolic blood pressure occurs due to the **elastic tissue in the aorta** and main vessels that stores the work of the heart in systole to maintain blood flow during diastole.

- ABP reflects cardiac output (CO) because **mean ABP = CO x systemic peripheral resistance**

Therefore, arterial blood pressure reflects organ and tissue perfusion.

In a patient with a normal or low peripheral resistance (e.g., with a warm, pink skin), a high blood pressure indicates a high cardiac output.

In a patient with a high peripheral resistance (e.g., with a cold, pale skin), a high blood pressure may not indicate a raised cardiac output.

Mean ABP = diastolic BP + 1/3 pulse pressure

$$\text{or Mean ABP} = \frac{\text{systolic blood pressure} + 2 \times \text{diastolic blood pressure}}{3}$$

N.B.: Pulse pressure = systolic blood pressure - diastolic blood pressure.

- The **most common** used **pressure units** in anesthetic practice are:

$$1 \text{ kPa} = 0.01 \text{ bar} = 7.6 \text{ mm Hg} = 10.3 \text{ cm H}_2\text{O}.$$

- **Factors Affecting Blood Pressure:**

1- The site of measurement:

Blood pressure varies with the site of measurement due to hydrostatic effects (figure 7-5).

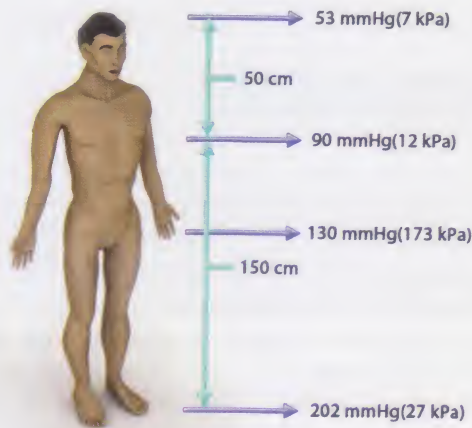


Figure 7-5: The effect of hydrostatic pressure on arterial blood pressure

Every 10 cm in height is equivalent to a pressure difference of 7.5 mmHg.

During standing, the mean arterial blood pressure may reach 53 mmHg (7 kPa) at the head,

90 mmHg (12 kPa) at the heart,

130 mmHg (17.3 kPa) at the finger,

and 202 mmHg (27 kPa) at the feet.

Therefore, a **standard reference point** is chosen that is the level of **the right atrium**.

2- The caliber of the blood vessel and its distance from the heart:

The blood pressure wave becomes narrower and increases in amplitude in peripheral arteries (due to change in their elasticities and presence of reflected waves) so that, even with the patient supine, the systolic and pulse pressure in the dorsalis pedis artery is higher than in the radial artery, which, in turn, is

higher than that in the aorta e.g., a dorsalis pedis artery pressure of 130/70 mmHg may be 110/80 mmHg in the aorta.

3- Diurnal variation:

Blood pressure is lower during sleep.

4- Respiratory cycle:

There is a decrease in systolic blood pressure during inspiration and increase during expiration. These changes are marked during intermittent positive pressure ventilation.

5- Anxiety and stress:

Both increase blood pressure; therefore, readings on 3 separate occasions may be required to obtain a representative value.

A) Non-Invasive Blood Pressure Monitoring (NIBP):

Indications:

It is used in all patients to be anesthetized, mostly every 5 minutes, as it is one of the standard II monitors. There are no contraindications except avoiding cuff application in limbs with a dialysis shunt or simply with intravenous lines.

Techniques:

1- Detection of Peripheral Pulsations

It is simple, but only gives an indication of the systolic pressure.

Technique:

- Blood pressure is measured by an inflatable cuff (first described by Scipione Riva-Rocci (1863-1937) in 1896 in Italy) placed on the upper or lower limb and connected to a manometer. It is called **Riva-Rocci cuff**.

The cuff is inflated to a pressure above the expected systolic pressure, and then it is slowly released at a rate of 2-3 mmHg/second. The systolic pressure is indicated by the reappearance of the peripheral pulse, which can be monitored by a detector.

- Detectors are one of the following:

- 1- **Manual palpation** of the radial or dorsalis pedis pulse.

- 2- **A pulse oximeter.**

- 3- **A plethysmography.**

- 4- **The flush method:** It is used in neonates, where the arm is raised and milked of blood and the cuff rapidly inflated and then slowly deflated. The systolic blood pressure is taken when a skin flush appears.

2- Auscultation Method of Korotkoff Sounds

Idea:

In 1904, Nicolai Sergivich Korotkoff (1874-1920), a surgeon, presented his methodology for measuring blood pressure in Saint Petersburg, Russia.

A sphygmomanometer is a device that is used to measure blood pressure (sphygmom is a Greek term for pulse and a manometer measures pressure).

On cuff deflation, **Korotkoff sounds** occur due to blood flow in stenosed vessels causing a turbulent flow which produces the sound (figure 7-6). The sound is detected by a stethoscope or a microphone.

It consists of:

- Phase I: 1st appearance of the sound i.e., onset of blood flow which equals the systolic blood pressure.
- Phase II: Sound is slightly muffled.
- Phase III: An increase in the sound volume.
- Phase IV: Abrupt fall in the sound; muffling again. It is sometimes considered the diastolic blood pressure (e.g., in hyperdynamic circulation as pregnancy, aortic incompetence, thyrotoxicosis, and exercise) where the sounds may not disappear until cuff pressure approaches zero.
- Phase V: Final loss of the sound. It is usually considered the diastolic blood pressure.

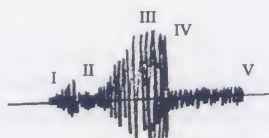


Figure 7-6: Korotkoff sounds

Precautions:**1- The cuff:**

- The cuff must be **positioned** so that the center of its bladder is **on the medial side** of the arm over the brachial artery.
- The **width** of the cuff should be **20% greater than the diameter of the arm** or equal to 2/3 the length of the upper arm (figure 7-7).

A too narrow cuff gives too high readings whilst a too wide cuff gives too low readings.

Recommended cuff widths are: 12-14 cm for an adult arm and 15-18 cm for an adult leg.

9 cm for 4-8 years.

6 cm for 1-4 years.

2-5 cm for neonate.

- The **length** of the cuff should be long enough to encircle the arm completely or at least 80% of the circumference of the upper arm (measured midway between the shoulder and elbow).

A short cuff causes readings to be too high whilst overlapping of a long cuff does not cause errors.

Recommended cuff length is 35 cm for adults, but the most common used length in adults is 23 cm.

- The cuff with its tubing and connections should **not leak**.
- **Miscuffing** is the term used to describe the use of inappropriate sized cuffs for blood pressure measurement. It is the most common cause of errors.

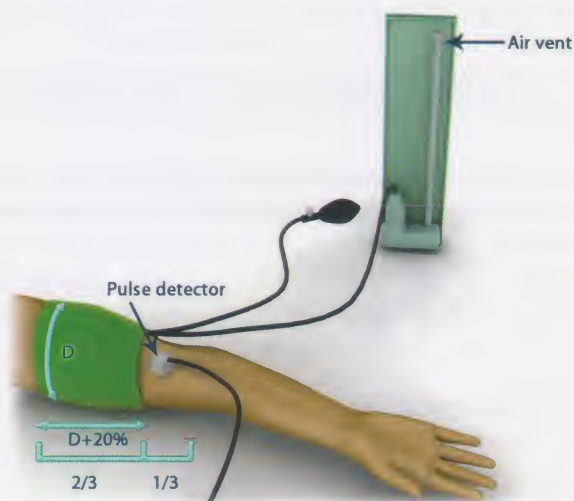


Figure 7-7: Cuff's position and width

2- Manometers:

- Aneroid gauge type should be calibrated regularly.
- Mercury column type should be used vertically and read zero before its use.

3- Stethoscope:

- It should be **placed** over the course of the artery i.e., **medially**. The bell-shaped head of a stethoscope is a low frequency transducer, while the flat, diaphragm-shaped head is designed to detect high frequency sounds. Therefore, **the bell-shaped head of the stethoscope** should be **used** to detect the low-frequency Korotkoff sounds (25-50 Hz). This is often neglected, and some stethoscopes are manufactured without a bell-shaped head.

- **Diasyst** is a specially molded rubber stethoscope that is secured under the cuff.

4- Auscultatory gap: It is the disappearance of Korotkoff sounds through part of the range from systolic to diastolic blood pressure. It may cause inaccurate reading.

3- The Doppler Technique**Idea:**

- A **piezo-electrical crystal** acting as an emitter and receiver of the ultrasound waves is placed, as a small Doppler probe, over an artery e.g., the brachial artery which lies distal to an occluding inflated cuff.

Doppler effect: When an ultrasound is directed to a moving structure, (e.g., red blood cells in the arteries), they reflect these ultrasound signals producing shift in their frequency which is proportional to the velocity of red blood cells.

- **On cuff deflation:**

At **systolic blood pressure**, blood starts to pass intermittently in the vessels and the vessel walls begin to move apart producing a certain shift in frequency. The sound frequency is within the audible range causing a characteristic loud high-pitched sound.

At **diastolic blood pressure**, no more movement is detected causing another characteristic sound pitch.

Arteriosonde:

- It is a more sophisticated device using **the same Doppler Effect**. The transducer crystal is attached to the surface of the cuff facing the subject's arm. This assembly (**the transducer and the cuff**) are positioned over the **brachial artery**. The cuff should be at the level of the heart. The transducer should be coupled to the skin by a layer of silicone gel, which prevents excessive sound reflections.

- The signals are similar in quality to the Korotkoff sounds, and both systolic and diastolic pressures can be determined during cuff deflation.

Advantages:

- 1- Accurate at low pressures and low cardiac output states e.g., shock.
- 2- Used easily in pediatrics and obese patients.
- 3- Effective in very noisy situations e.g., helicopter transport.

Disadvantages:

- 1- Affected by presence of air, so a coupling gel (but not corrosive electrode jelly) must be applied between the probe and the skin.
- 2- Correct positioning of the probe directly above the artery is crucial, since the beam must pass through the vessel wall.
- 3- Interference occurs from probe movement, dysrhythmias, or diathermy.

4- Oscillometry

Idea:

It uses the principle of **plethysmography** to detect pulsatile pressure changes (oscillations) in an underlying artery.

As the BP cuff is deflated from above, **oscillation** in the cuff pressure occurs (like the oscillations in a mercury column or an aneroid gauge needle) (figure 7-8).

Onset of oscillation = **Systolic** blood pressure.

Maximum of oscillation = **Mean** blood pressure.

Offset of oscillation = **Diastolic** blood pressure.

Automated oscillometer (known as a noninvasive blood pressure "**NIBP**" monitors) consists of (figure 7-9):

- A microprocessor that controls the inflation and deflation sequence.
- An air pump that inflates a single cuff. The cuff is inflated either to a high initial value e.g., 180 or 200 mmHg or in repeated readings, it is inflated to 25 mmHg above the previous systolic measurement.
- A bleed-valve that deflates the cuff at a rate of 2-3 mmHg/sec.
- A pressure transducer that records the oscillating pressure signals which in turn are interpreted by the microprocessor.
- 2 tubular connections are connected to the cuff, one for inflation of the cuff and the other senses (detects) the pressure fluctuations and transmits them to the pressure transducer.

Other models have a single external tube which is divided into 2 tubes inside the device.

N.B.: The first instrument to use this principle was called a **device intermittent noninvasive automated mean arterial pressure "Dinamap"**.

N.B.: **Von Recklinghausen Oscillotonometer:**

It is an old model (1931) where 2 cuffs were present, a proximal one for occluding the blood vessel, and a distal cuff for detecting the pulsations. Both systolic and diastolic blood pressures were detected by needle oscillations.

Disadvantage:

- 1- It is **inaccurate** at - Low systolic blood pressure < 60 mmHg e.g., shock or heart lung machine.
 - High systolic blood pressure as it underestimates it.
 - Period of dysrhythmias.
 - Obese patients with unsuitable cuff size.
 - Patient's movements.
- 2- It is **not suitable for rapid changes of blood pressure** as one reading takes one minute. Even at this rapid rate, it may impede blood flow.

- 3- Complications of **repeated cuff inflations** may occur as ulnar nerve injury, petechial hemorrhage, and extravasation of intravenous fluids.
- 4- Backflow of blood into intravenous cannulas.

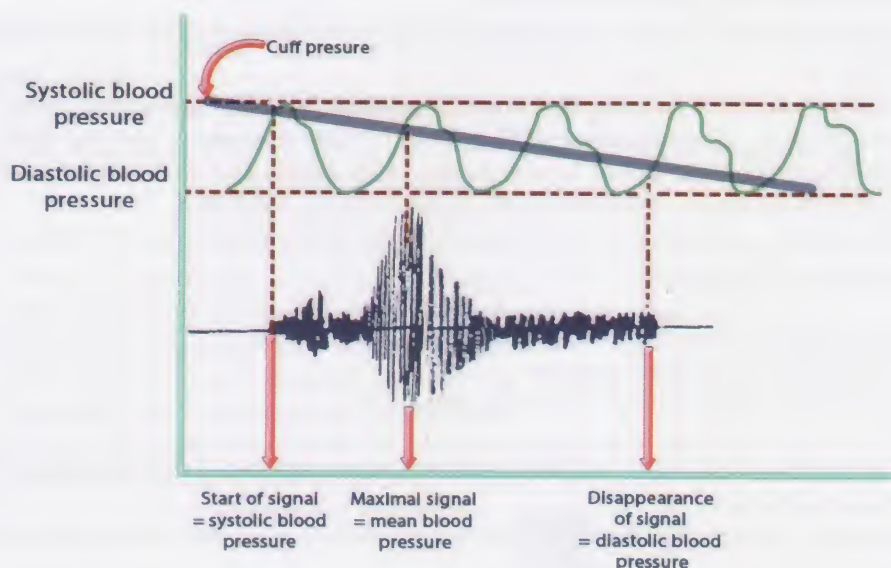


Figure 7-8: Oscillometry

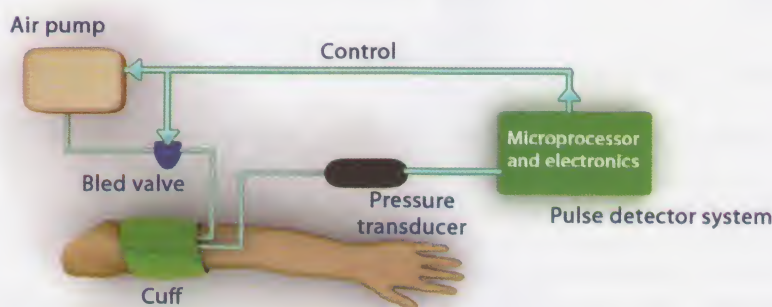


Figure 7-9: An automated oscillometer

5- Finapres or Penaz Technique (Finometer)

Finapres: Fin i.e., finger, a i.e., arterial, pres i.e., pressure.

Idea:

It is a **continuous** NIBP monitoring.

N.B.: The word "continual" is defined as "repeated regularly and frequently in steady rapid succession" whereas "continuous" means "prolonged without any interruption at any time".

A cuff is placed around a finger and rapidly inflated and deflated by a high-speed servo-pump to a pressure just less than that which causes the digital artery to collapse. This pressure is called "**the zero transmural pressure**" (figure 7-10).

As the pressure changes, the volume of the blood in the artery changes. This change in volume is sensed by an **infrared light-emitter** (that emits infrared light) and **photo-electric receivers** (that receive the transmitted light), both are present **in the cuff**. They act as a photo-plethysmograph, which operates a **high-speed solenoid controlled air servo-pump**, which then adjusts the cuff inflation to maintain zero transmural pressure.

Therefore, the cuff pressure reflects intra-arterial pressure at all times. These pressure signals are transmitted to a transducer, and a waveform similar to the invasive arterial pressure wave is displayed on a screen.

As with all finger cuff methods, the cuff should be at the level of the heart.

Disadvantages:

- 1- It is less accurate than invasive blood pressure. It only correlates with invasive blood pressure at systolic blood pressure, but not at diastolic and mean blood pressure (the same accuracy of oscillometry).
- 2- The finger cuff must be properly positioned.
- 3- The pneumatic transducer is cumbersome and must be placed at the level of the right atrium.
- 4- It is unreliable with poor peripheral circulation: as
 - peripheral vascular diseases,
 - hypothermia,
 - and • prolonged that use causes vasoconstriction.
- 5- Due to continuous pressure applied in the cuff, the finger tends to become blue, congested, and painful after 30-40 minutes use and ischemic damage may occur. Therefore, deflating the cuff for several minutes every 30 minutes is recommended.

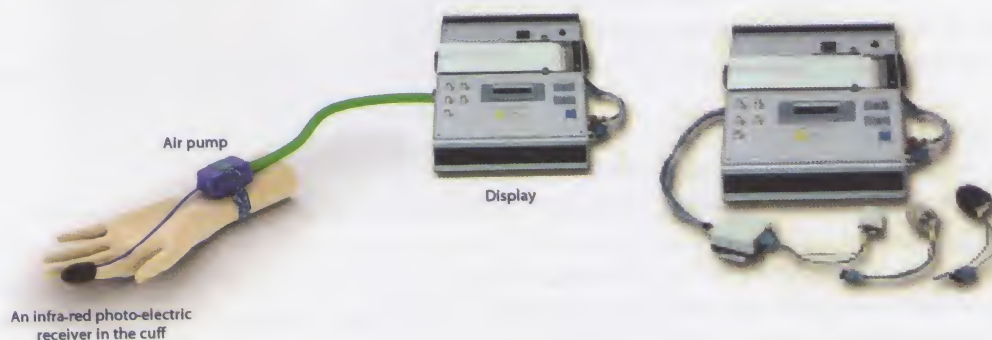


Figure 7-10: Finapres cuff and pneumatic transducer strapped to the forearm and the display module

6- Arterial Tonometry (Radial Artery Compression):

Idea:

It gives a **continuous** NIBP monitoring.

The instrument contains **pressure sensors (pressure transducers)** which are strapped to the wrist and applied on the skin over the radial artery. The pressure sensors are connected to a **hydraulic control system** which applies pressure to the wall of the radial artery to make the artery partially flattened against the underlying bony structure of the radius bone (figure 7-11).

When the pressure over the radial artery (produced by the hydraulic system) is increased steadily at the sensors, the **pressure fluctuations** increase, then reach a maximum, and then the fluctuations decrease, in a **similar manner** to the pulsations observed in the **automated oscillometry**. The pressure sensors detect these fluctuations and display the changes in pressure as a **waveform**. Therefore, the systolic, mean, and diastolic blood pressure can be detected.



Figure 7-11: An arterial tonometry

Disadvantages:

- 1- It is affected by motion of the limb and should be positioned carefully.
- 2- It needs frequent calibration.

B- Invasive Blood Pressure Monitoring

It is the **gold standard** for arterial blood pressure measurement. It provides **continuous** beat to beat pressure measurement.

Indications:

- 1- Anticipation of wide intraoperative **blood pressure swings** e.g.,
 - Cardiothoracic surgery.
 - Major vascular surgery.
 - Surgery for pheochromocytoma.
 - Neurosurgery.
 - Major organ transplantation as heart, lung, kidney or liver.
- 2- **Elective hypotension.**
- 3- **End organ disease** requiring beat to beat blood pressure regulations e.g.,
 - Critically ill patients and shocked patients.
 - Inotropic therapy.
- 4- **Inability to record NIBP** e.g.,
 - very obese patients.
 - very extensive burns.
- 5- The need of multiple **arterial blood gases** analysis (ABG analysis).

Recently, fiberoptic O₂ sensor (optode) can be inserted via the arterial cannula to assess oxygenation (see later).

Contraindications:

- 1- **Arteries without** documented **collateral** blood flow.
- 2- **A limb** with suspicion of preexisting **vascular insufficiency** e.g., Raynaud's phenomenon.

Technique:

An artery (usually a peripheral one as the radial artery) is cannulated and connected by a tubing system containing saline to a pressure transducer (usually a diaphragm type). The final pressure waveform produced may be displayed on an oscilloscope.

The following steps are done:

a) Selection of an Artery for Cannulation:

- 1- **The radial artery:** is the most common one used especially in the non-dominant hand. Ulnar collaterals should be tested by
 - a- **Allen's test:** 1st described by Allen in 1929 to test collaterals in patients with thrombo-angitis obliterans.
 - It is not completely reliable (it has a sensitivity of 87%) and needs patient cooperation.
 - The patient exsanguinates the hand by making a fist. If the patient is under anesthesia, a 3rd person can squeeze the hand.
 - While the operator occludes the radial and ulnar arteries with finger tip pressure, the patient relaxes the clenched fist.
 - When the pressure on the ulnar artery is released, flushing of the thumb occurs.
- If it occurs within 5 sec after pressure release, this indicates good collaterals i.e., a positive test.
 If it occurs within 5-10 sec after pressure release, this indicates an equivocal test.
 If it occurs after 10 sec after pressure release, this indicates insufficient collaterals i.e., a negative test.
 If the ulnar artery is to be cannulated, the test is performed similarly, but pressure is released over the radial artery first.

- b- **Alternative methods**, without patient cooperation.

As blood flow distal to the radial artery occlusion can be detected by **palpation**, **Doppler probe**, **plethysmography**, or **pulse oximetry**.

- 2- Other arteries can be used as ulnar artery, brachial artery (there are usually many collateral vessels at the elbow, but it may cause median nerve injury), dorsalis pedis artery, posterior tibial arteries and femoral artery. A peripheral artery should be chosen so that if a clot or hematoma occurs, the whole limb is not threatened.

b) Technique of Arterial Cannulation (e.g., radial artery) (figure 7-12).

- Supination and extension of the wrist to provide optimal exposure of the radial artery is done.
- The pressure-tubing-transducer system should be nearby and already flushed with heparinized saline (0.5-1.0 unit of heparin per mL of saline).
- The radial pulse is palpated and the artery's course is determined by lightly pressing the tips of the index and middle fingers.
- After preparing the skin with iodophor and alcohol solution, 0.5 mL of **lidocaine** is **infiltrated** directly above the artery with a 25-27 gauge needle in the conscious patients.
- A 20-or 22- gauge **Teflon cannula**-over-needle assembly penetrates the skin at a 45- degree angle and is directed towards the point of palpation. Teflon decreases the risk of arterial thrombosis.

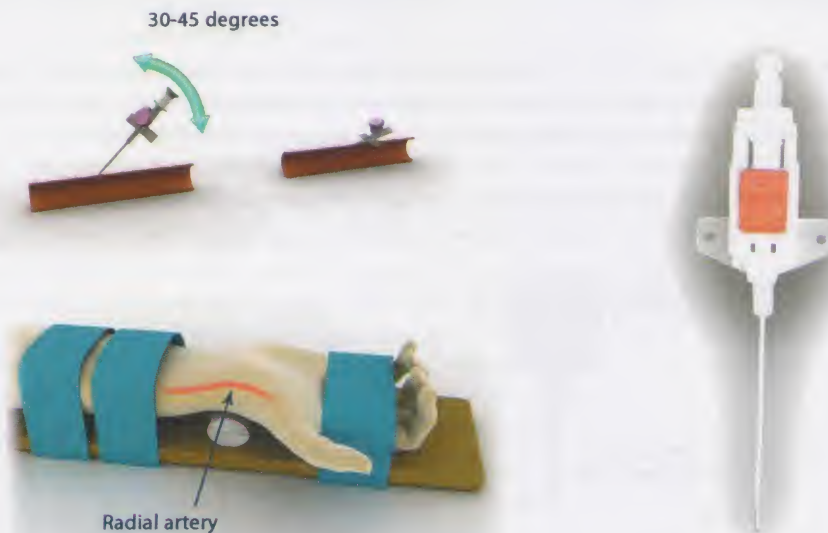


Figure 7-12: Technique for arterial line placement (left) and an arterial cannula with a locker (right)

- Upon blood flashback, the needle is lowered to a 30-degree angle and advanced another 2 mm to make certain that the tip of the catheter is well inside the vessel lumen.
- The catheter (cannula) is advanced over the needle which is then withdrawn.
- Sometimes the radial artery is tortuous and the cannulation becomes difficult; therefore, a technique utilizing a **flexible guide-wire** is often more successful because this can negotiate the bends more easily than the standard cannula.
- Applying pressure with the middle and ring fingertips prevents blood spurting while the tubing is **firmly connected using Luer lock** connections to avoid occurrence of a leak with risk of fatal blood loss.
- Waterproof tape or suture is used to keep the catheter in place to avoid fatal blood loss.
- The cannula is connected by a stopcock and saline filled high pressure tubing to a transducer which is a diaphragm (strain) gauge type causing stretch of wire or silicone crystals (figure 7-13). This causes a change in its electrical resistance which affects the Wheatstone bridge circuit. The voltage output is proportionate to the pressure applied to the diaphragm.

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Figure 7-13: An arterial pressure transducer (right) and the pressure transducer connected to the patient via a connection line filled with saline (left).

• **Flushing of the cannula** is mandatory to avoid clotting and obstruction of the cannula. Flushing is done by either:

- **Intermittent** flushing technique with heparinized saline as above through a three-way tap using a syringe. The high pressures generated by small syringes can damage arterial walls or the diaphragm of the pressure transducer. Therefore, syringes smaller than 5 mL should not be used.
- **Continuous** flushing technique (figure 7-14) is preferred if long-term recording is needed. The heparinized saline used is kept in a pressurized container at a pressure above systolic pressure. It then passes from the container through a constriction adjusted so that the flow does not exceed 4 mL/hour.

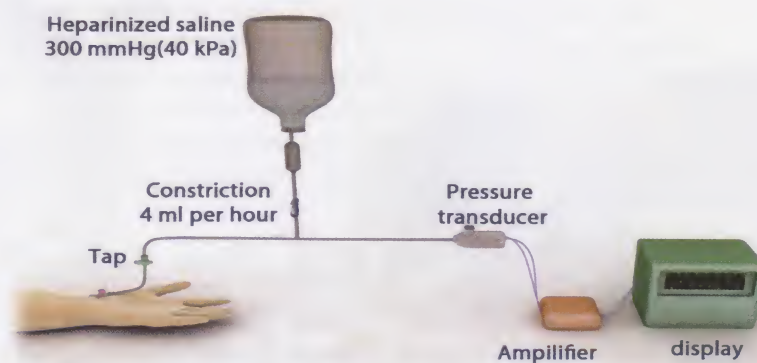


Figure 7-14: Continuous flushing system

c) Transducer Zeroing:

A transducer is put at the level of the desired point of measurement.

- **Systemic BP:** in a supine patient at **mid-axillary** line.
- **Cerebral BP:** in a seated patient at the ear (it represents pressure of circle of Willis).

The stopcock is opened exposing the diaphragm and the saline to the atmosphere but the line connected to the patient is closed. The zero is readjusted when the monitor is switched on.

N.B.: Change in patient's position e.g., lowering or raising the operation table necessitates readjusting the position of the diaphragm transducer and re-zeroing at the new mid-axillary line.

Fiberoptic Catheter Tip Transducer

Idea: It is a new technique where a small diaphragm transducer is fixed on the tip of an intra-arterial catheter. The diaphragm is mirror coated. An optical fiber is present which directs light to the mirror of the diaphragm. The movement of the diaphragm, which changes in response to changes in pressure, determines the fraction of the reflected light which is detected by another optical fiber acting as a light receiver. The other end of the catheter connects to an optoelectric module, which converts the light into an electrical signal which in turn is interpreted in terms of pressure (figure 7-15). It is very expensive.

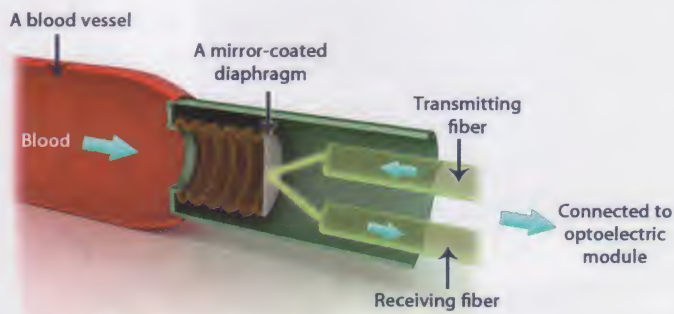


Figure 7-15: Catheter tip transducer

Value of Arterial Cannulation:

1- It is more **accurate** than NIBP as: Systolic blood pressure is 5 mmHg higher than NIBP.

Diastolic blood pressure is 8 mmHg lower than NIBP.

It is a reliable method **during hypotension or shock** unlike the NIBP which usually fails to record blood pressure below a certain limit.

2- The **shape of the arterial waveform** can give indications as follows:

- The rate of the upstroke indicates **contractility**.
- The rate of the downstroke indicates **peripheral vascular resistance**.
- Exaggerated variations in size during respiration or with mechanical ventilation indicate **hypovolemia (i.e., decreased preload)**. If the systolic blood pressure during expiration is > 10 mmHg higher than that during inspiration, this is called **pulsus paradoxus** which occurs in cardiac tamponade, tension pneumothorax and severe bronchospasm.
- **Area under the pressure curve** indicates **mean arterial blood pressure**.
- **Arterial waveform contour analysis** indicates cardiac output because the rate at which blood flows from arteries to veins (i.e., cardiac output) is proportional to the rate of fall of blood pressure.
- The **dicrotic notch** is due to intra-aortic vibrations caused by closure of the aortic valve.
- As the pressure wave moves towards the periphery (i.e., at femoral and radial arteries), the systolic pressure gradually increases (up to 20 mm Hg) in relation to that of the proximal vessels (e.g., aorta and brachial arteries), but with narrowing of the systolic pressure wave; therefore, the mean arterial pressure remains unchanged and is a more accurate measure of central aortic pressure.

The quality of the waveform: depends on the dynamic characteristics of the catheter-tubing-transducer system (figure 7-16).

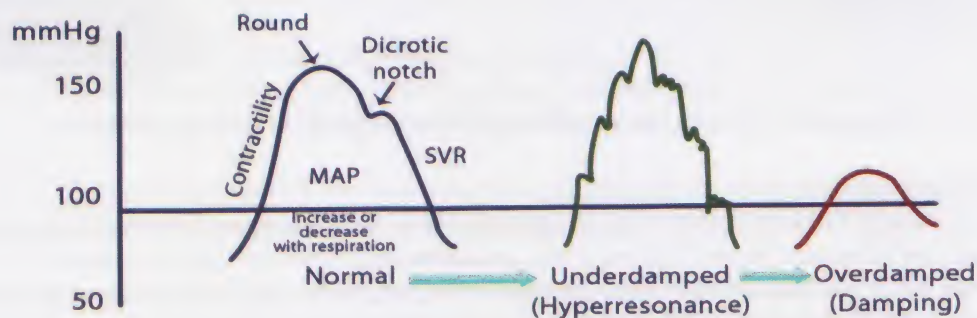


Figure 7-16: Arterial waveform

a) Hyper-Resonance (Under-Damping):

- Movement of the diaphragm of the pressure transducer converts blood pressure changes into electrical signals. These movements are associated with very small movements of saline to and fro along the catheter with pressure changes (as a weight on the end of a spring).
- They will oscillate at a particular frequency called the **natural resonant frequency**.
- The **arterial pulse natural resonant frequency is usually between 0-40 Hz**. If the resonant frequency of this system falls within the frequency of arterial pulsation, these oscillations make a sine wave which superimposes on the BP waveform causing distortion of the BP waveform.
- Most diaphragm transducers have frequencies of several hundred Hz (usually > 200 Hz), but the addition of tubing and stopcocks, and air in the line decreases the frequency of the system and may reach < 40 Hz which is not wanted. Therefore, the natural resonant frequency of the system should exceed that of the arterial pulse and thus not to be recorded by the pressure module. This occurs by:
 - 1- Decreasing tube or catheter length (compared with an old model catheter).
 - 2- Increasing tube or catheter width (compared with an old model catheter).
 - 3- Using a stiffer tube or catheter (i.e., lower compliance) (compared with an old model catheter).
 - 4- Eliminating unnecessary stopcocks.
 - 5- Removal of air bubbles.
 - 6- Using a low-volume displacement diaphragm (figure 7-17).

b) Damping (Over-Damping):

It occurs when the blood pressure changes are not transmitted from the artery to the diaphragm transducer where the displayed blood pressure waveform will be damped and the sharp changes occurring in BP are not transmitted to the system and thus are not displayed. Therefore, the size of the measured waveform will be less than the actual blood pressure.

This occurs when a **restriction is present in the diaphragm-tubing system** e.g.,

- Air bubbles, in the system, which absorb the pressure changes in the saline column.
- Kinking of the cannula.
- Arterial spasm.
- Clot formation in the cannula.



Figure 7-17: Shorter wider stiffer tube without stopcocks or air bubbles

Complications of Arterial Cannulation:

- 1- Hematoma formation such as in the wrist (radial artery) or retroperitoneal area (femoral artery).
- 2- Vasospasm and ischemia of tissues distal to the puncture site.
- 3- Thrombosis: although thrombosed arteries appear to re-canalize by time, many patients have decreased pulsations in an artery which has been cannulated and subsequent cannulation of the same artery or a distal branch may lead to inaccurate recordings of BP.
- 4- Embolization of air bubbles that may cause loss of a digit.
- 5- Skin necrosis overlying the catheter.
- 6- Nerve damage.
- 7- Infection.
- 8- Disconnection causing fatal blood loss.
- 9- Inadvertent injection of drugs (may lead to distal gangrene).
- 10- Skills are required to insert the cannula.
- 11- Heparin-induced thrombocytopenia (for heparin-flushed lines).
- 12- Late development of fistula or aneurysm.

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V- Central Venous Catheterization

Indications:

- 1- **Fluid management** in - hypovolemia and shock,
and - surgeries with expected large fluid shift e.g., splenectomy or open cardiac surgery....etc.
- 2- **Infusion of:** - caustic drugs as chemotherapy,
- total parenteral nutrition (TPN),
and - fluids or blood if large amounts are needed.
- 3- **Aspiration of** air embolism.
- 4- **Insertion of:** - transvenous pacemaker.
- pulmonary artery floatation catheter.
- 5- **Venous access in:** - patients with poor peripheral veins.
- hemofiltration and hemodialysis.
- plasmapheresis.

N.B.: For measurement of right atrium pressure or aspiration of air emboli; the tip of the cannula should be at the junction of the superior vena cava (SVC) and right atrium, assessed by chest X-ray.

Contraindications:

- 1- Renal cell tumor extension into the right atrium.
- 2- Fungating tricuspid valve vegetations.
- 3- At the site of the cannula as internal jugular vein cannulation e.g.,
 - Patients receiving anticoagulants.
 - Ipsilateral previous carotid endarterectomy (due to risk of carotid artery puncture).

Value of Central Venous Pressure (CVP) Measurement:

Normal Range: It differs according to the zero reference point.

• Normal central venous pressure value is **-4 to +10 mmHg (-5.4 to +13.6 cmH₂O)** when the **zero reference point** for venous pressure in the thorax is a point on the external thorax where the **4th intercostal space intersects the mid-axillary line** (i.e., the line midway between the anterior and posterior axillary folds). This point (called the **phlebostatic axis**) corresponds to the position of the right and left atria when the patient is in the **supine position**. It is **not a valid reference point in the lateral position**; therefore, central venous pressure and pulmonary capillary wedge pressure should not be recorded when patients are placed in lateral positions.

• Central venous pressure value is lower than the above normal range by 5-10 cm H₂O when the manubrio-sternal junction is used as the reference point.

CVP varies with: ventilation because transthoracic pressure is transmitted through the pericardium and thin-walled venae cavae.

• In **spontaneous respiration:** During **inspiration**, the negativity of intra-thoracic pressure increases due to expansion of the thoracic cavity. This negative pressure is transmitted to the relatively thin walled right atrium and venae cavae causing a **decrease of CVP**. The reverse occurs during expiration causing an increase of CVP.

• In controlled **mechanical ventilation:** The situation is reversed as during **inspiration**, the positive pressure increases the intrathoracic pressure and **elevates CVP by about 5 cm H₂O**.

Therefore, **CVP measurements are best performed and compared at the end of expiration**. When positive end-expiratory pressure (PEEP) is applied, the positive pressure is transmitted to the right atrium, causing a decrease in venous return and a rise in CVP again. Removal of PEEP during CVP measurement is not advised.

CVP gives information about:

- Intravascular **blood volume**.
- **Venous return**.
- **Right atrial pressure** which reflects **right ventricular end diastolic volume** which in turn reflects **right ventricular function**.

CVP measurement is only of value if:

1- It is used **in combination with other measures and clinical signs** e.g., arterial blood pressure, heart rate, urine output, and body temperature.

2- **The trend of values** is compared which is **more important** than absolute values e.g., fall of CVP from +5 to +1 cm H₂O indicates large fluid loss although both are normal values.

3- **A fluid challenge test** is performed: If a young patient with an increased CVP receives 100- 200 mL intravenous fluid, two possibilities may occur:

- The CVP decreases which indicates hypovolemia, yet the CVP was high due to severe sympathetic stimulation that caused venous vasoconstriction.
- The CVP increases more which indicates heart failure, yet the CVP was high due to decreased cardiac pump action.

4- **Obtaining a blood sample to detect hypoxia:**

- True mixed venous O₂ saturation (S \bar{v} O₂) must be measured in the pulmonary artery. S \bar{v} O₂ reflects the relative delivery of O₂ to the tissues compared with consumption.
- Central venous O₂ saturation (ScvO₂) does not require a pulmonary artery catheter, but theoretically, the value will differ from S \bar{v} O₂ because ScvO₂ obtained from a subclavian or internal jugular vein does not reflect venous blood returning via the inferior vena cava or coronary sinus. Generally, ScvO₂ is about 5% higher than S \bar{v} O₂. In practice, ScvO₂ appears to have similar predictive value for end-organ hypoxia as S \bar{v} O₂.

b) Normal Shape:

CVP waveform is related to right atrial pressure changes (figure 7-18).

	Cause	ECG Related	Phase (Time at which the wave begins)
a wave	• Due to <u>A</u> trial contraction (<u>A</u> trial kick).	With P wave	End of diastole
c wave	• Due to isovolemic (isometric) right ventricular <u>C</u> ontraction which closes tricuspid valve cusps causing it to bulge into the right atrium. This increases right atrial pressure.	After onset of QRS complex	Early systole
x wave (x descent)	• Due to atrial relaxation and changing atrial geometry produced by downward displacement of right ventricle during its contraction.	With ST segment and T wave	Systole
v wave	• Due to <u>v</u> enous filling (<u>v</u> enous return) of the right atrium against a closed tricuspid valve during isometric relaxation phase of the right ventricle.	After T wave	Late systole
y wave (y descent)	• Due to tricuspid valve opening with emptying of the right atrium to fill the right ventricle.	After T wave to the onset of P wave	Diastole

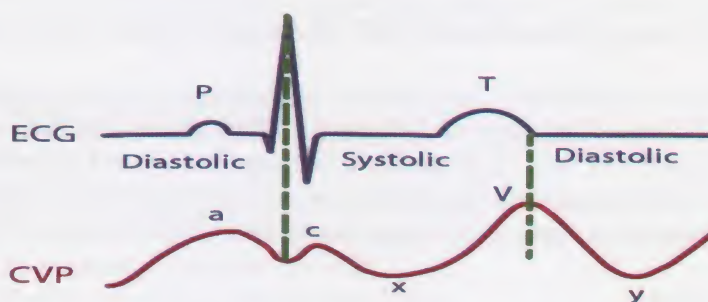


Figure 7-18: The relationship between CVP and ECG

Central Venous Pressure (CVP) Diagnostic Details (Detected From the Waveform)

1. Tachycardia:

Tachycardia causes **fusions** of waves together (figure 7-19).

Bradycardia:

It causes **separation** between waves.

Separation between "a" and "c" waves produces "x" descent.

Separation between "v" and "a" waves produces a mid to late diastolic plateau (**h wave**) which occurs after y descent and before the "a" wave (figure 7-20).

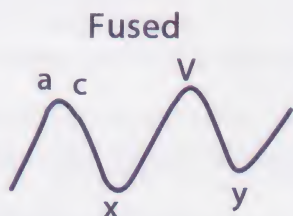


Figure 7-19: CVP with tachycardia

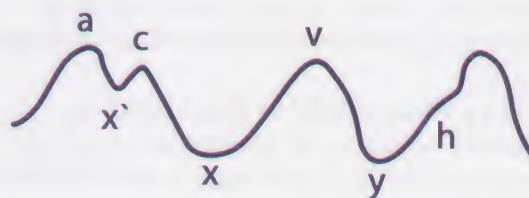


Figure 7-20: CVP with bradycardia

2. Dysrhythmias:

a) Atrial Fibrillation (AF):

No atrial contraction occurs, this causes **disappearance of "a" and "x" waves, but prominent "C" wave** because atrial volume is greater at end of diastole and onset of systole. Sometimes, **fibrillation waves** are seen on the CVP trace (figure 7-21).

b) Junctional Rhythm:

Atrial contraction will occur with ventricular contraction when the tricuspid valve is closed (instead of atrial contraction preceding ventricular contraction). This produces **tall canon a wave** (figure 7-22).

c) Ventricular Pacing:

Ventricular pacing produces atrio-ventricular dissociation, which produces **tall canon a wave** (figure 7-22).

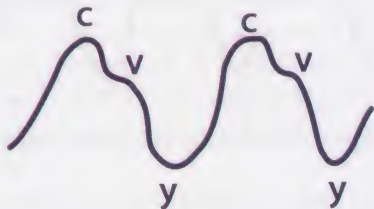


Figure 7-21: CVP with atrial fibrillation

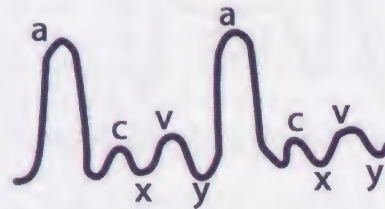


Figure 7-22: CVP with junctional rhythm or ventricular pacing

3. Tricuspid Valve Disease:**a) Tricuspid Regurgitation:**

It produces abnormal systolic filling of the right atrium from the right ventricle via the incompetent valve. This produces **broad and tall "C" and "V" waves and obliterates "x" descent**, so the right atrial pressure resembles right ventricular pressure. The CVP waves are called **ventricularized CVP tracing** (figure 7-23). In a similar manner, a tall systolic "c" and "v" waves are noted in the pulmonary artery wedge pressure in severe mitral regurgitation.

b) Tricuspid Stenosis:

It produces a diastolic defect in atrial emptying on filling the right ventricle i.e., impairment of diastolic descent of blood from the right atrium to the right ventricle. This elevates the mean CVP and causes a **prominent "a" wave and slurred attenuated "y" descent** (figure 7-24).

N.B.: Pulmonary hypertension causes a prominent "a" wave, but does not attenuate the "y" descent.



Figure 7-23: CVP with tricuspid regurgitation

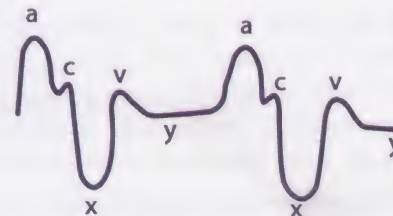


Figure 7-24: CVP with tricuspid stenosis

4. Right Ventricular Ischemia and Infarction:

Atrial contraction occurs against a stiff right ventricle; therefore, the CVP is increased and a **prominent "a" wave is produced**. **Tricuspid regurgitation occurs; therefore, a prominent "v" wave is produced** (figure 7-25). In a similar manner, pulmonary capillary wedge pressure is changed in left ventricular ischemia and infarction.

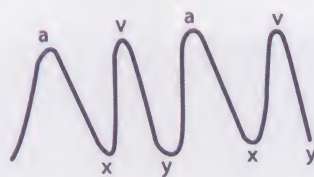


Figure 7-25: CVP with right ventricular ischemia and infarction

5. Pericardial Constriction:

It decreases venous return and cardiac output; therefore, CVP is increased. CVP tracing will resemble that of right ventricular infarction due to prominent **"a" and "v" waves and steep "x" and "y" descents i.e., M or W configuration**. Often the steep "y" descent (dip) is short lived. A mid-diastolic plateau wave (h wave) occurs giving a **square root sign or Friedreich's sign** because diastolic blood flow from the atrium

to the ventricle is initially rapid (steep y descent) then abruptly stops by the restrictive pericardial shell (plateau or h wave) (figure 7-26).

6. Cardiac Tamponade:

It produces **prominent x descent**, but **absent y descent**, because the diastolic flow of blood from the right atrium to the right ventricle is impaired by the compressive pericardial fluid collection (figure 7-27).

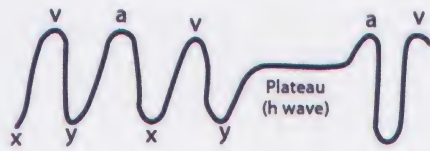


Figure 7-26: CVP with pericardial constriction

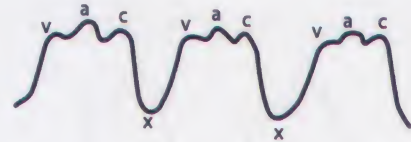


Figure 7-27: CVP with cardiac tamponade

Differences between Right Atrium and Left Atrium Venous Waveforms: (figure 7-28)

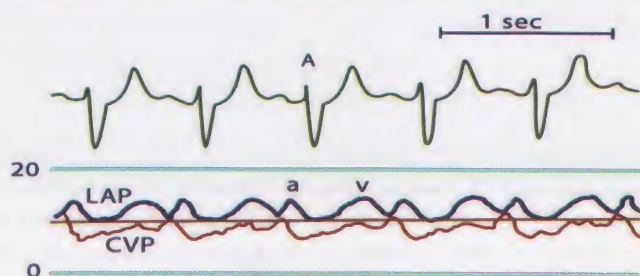


Figure 7-28: Venous waveforms of the right and left atria; left atrial pressure (LAP) and central venous pressure (CVP)

- The mean left atrial pressure exceeds the mean right atrial pressure.
- The left atrial "a" wave begins slightly after the right atrial "a" wave (by approximately 20 msec) because atrial depolarization begins in the SA node located near the junction of superior vena cava and right atrium.

Also, the left atrial "c" wave slightly precedes the right atrial "c" wave, because left ventricular isometric contractions and mitral valve closure occur first. Therefore, left atrium "a" and "c" waves tend to merge and become less distinct than their counterparts in the right atrium.

- "a" wave tends to be the most prominent wave in the right atrium pressure trace, while the v wave is generally the most prominent wave in the left atrium.

In right atrium venous waveform, (a---cv)

In left atrium venous waveform, (ac---V)

Differences between PCWP and Left Atrial Venous Waveforms:

PCWP is delayed (by 150-200 msec). It is a damped reflection of left atrial pressure.

Technique of Central Venous Catheterization:

- **Antiseptic measures** should be taken such as **handwashing** with an antimicrobial soap or gel, wearing **sterile gloves** (for central and arterial catheters), and wearing **masks, sterile gowns, and sterile drapes**. Nonsterile disposable gloves are enough for cannulation of peripheral veins. The skin at the site of insertion should be decontaminated with an **antiseptic agent** such as chlorhexidine, povidone iodine (Betadine) or 70% alcohol. These agents should be **allowed to dry on the skin** and not wiped off to maximize their antibacterial effects (figure 7-29).



Figure 7-29: Sterile technique for central line insertion

• **Catheter types:**

1- **Polyurethane catheters:** are designed for short-term cannulation (**days**). Polyurethane is a synthetic polymer known for its strength, durability, and moisture resistance.

2- **Silicone catheters:** are designed for prolonged use (**weeks to months**). Silicone is a synthetic polymer known for its flexibility and its resistance for thrombogenicity.

3- **Heparin-Bonded catheters:** Some new catheters are available with a heparin coating **on the external surface** to prevent thrombus formation and thus, decrease the incidence of catheter-related infections (thrombosis increases the incidence of infection as the microorganisms become trapped and proliferate in the fibrin meshwork of a thrombus). There are some reports that heparin-bonded catheters can cause **heparin-induced thrombocytopenia** (due to washing away of the heparin coating within a few hours by the flow of blood outside the catheter); therefore, some authors do not recommend the use of these catheters.

4- **Antimicrobial-impregnated catheters:** These catheters have antimicrobial bonding on both (outer and inner) surface. The antimicrobial coating is either, a combination of chlorhexidine and silver sulfadiazine (its activity lasts one week) or a combination of minocycline and rifampin (its activity lasts up to 4 weeks). They are used in neutropenic patients and burn patients.

5- **Peripherally inserted central catheters:** They are long catheters (50-60 cm) which can be inserted in the basilica vein or cephalic vein in the arm and advanced into the superior vena cava. They are made of soft silicone rubber, and a guidewire is required to insert them. They have the advantages over central cannulation as there is no risk of pneumothorax (figure 7-30).



Figure 7-30: A peripherally inserted central catheter

Other Intravenous Catheters:

6- **Implanted ported catheters (Porta-cath):** They are inserted, like the central venous catheters, but they have titanium implantable port that is connected to the radiopaque silicon catheter. The catheter is tunnelled under the skin and the port is hidden in a pocket in the subcutaneous tissues (i.e., the port and the catheter are completely present in the subcutaneous tissues). There is a rubber diaphragm in the port that allows a needle to be introduced through it. It is used for repeated long term injections such as chemotherapy. It is not suitable for central venous pressure measurement, blood sampling, or drug infusion (figure 7-31).



Figure 7-31: Implanted ported catheters (Porta-cath)

7- Long-term dialysis catheters (Hemo-cath or prima-cath): They are silicon catheters designed for long-term dialysis and for veno-venous hemofiltration. They are inserted into a central vein (usually internal jugular or subclavian vein) by a Seldinger technique (figure 7-32).



Figure 7-32: A long-term dialysis catheter

8- Peripheral intravenous catheter or cannula: They are available in 26 (violet), 24 (yellow), 22 (dark blue), 20 (pink), 18 (green), 16 (grey), 14 (orange), and 12 (light blue) gauge.

• **Catheter size and length:**

- The catheter size is expressed in either French size or gauge size (the differences between them are discussed in the appendix at the end of this book).
- The flow through the catheters depends on **Hagen-Poiseuille formula** which is discussed in details in chapter "Basic Physics for Anesthesia & Intensive care". From the formula, it is estimated that to get the most appropriate catheter **for rapid infusion, short catheters with large diameters** should be used where **catheter diameter takes precedence** over catheter length when rapid infusion is needed.
- Central venous catheters are designed for cannulation of the subclavian vein, the internal jugular vein, or the femoral vein. They are much longer than catheters used to cannulate peripheral veins and are typically 15-25 cm (6-10 inches) in length as compared to the peripheral catheters which are usually 5 cm (2 inches) in length. Central catheters are available with one, two, three, or more separate infusion channels, which are advantageous when multiple medications are required (figure 7-33).



Figure 7-33: A single, double, triple- and multiple-lumen central venous catheters, a set for central venous catheter

- **Local anesthesia infiltration** is performed in central and arterial catheters.
- **Techniques of catheter insertion:** There are two techniques:
 - a- **Catheter-over-needle technique:** it is usually used for peripheral cannulation and sometimes for central cannulation. When the tip of the needle enters the blood vessel (and the blood fills the flush chamber), the catheter is advanced over the needle and into the lumen of the vessel (figure 7-34).



Figure 7-34: A peripheral catheter or cannula (gauge 20) (a catheter-over-needle device)

b- Catheter-over-guideline technique (Seldinger technique):

Seldinger invented and introduced this technique in the early 1950s. It is easier, surer and less traumatizing than catheter-over-needle technique in central venous catheter insertion.

A **small-bore needle** (usually 20 gauge) is used to probe for the target vessel. When the tip of the needle enters the vessel, a **long, thin guidewire** with a flexible curved tip is passed through the needle and into the vessel lumen with little resistance. The needle is then removed while holding the guidewire and a **rigid dilator catheter** is first threaded over the guidewire to create a tract. Never let the guidewire go as it may be introduced totally inside the vein and require surgical removal. If a resistance is met during introduction of the guidewire, remove both the guidewire and the needle simultaneously to avoid cutting of the guidewire by the tip of the needle and then try again.

After insertion of the guidewire, the dilator is removed and a **catheter** is advanced over the guidewire while holding the guidewire and into the blood vessel to the desired tip location. Sometimes, two dilators are used with different sizes to facilitate insertion of a large sized catheter. Once in place, the catheter is fixed to the skin with a single suture and covered by a suitable dressing.

Sometimes, an **introducer catheter** (usually 9 French gauge) with a side-arm infusion port (figure 7-35) is inserted over the guidewire where a central venous catheter can then be threaded through the introducer catheter. The value of the introducer catheter:

- It allows central venous catheters and swan ganz catheters to be inserted and removed repeatedly without a new venipuncture.
 - Its side-arm infusion port can be used as a stand-alone infusion device particularly when rapid infusion rates are necessary.
- **After insertion, obtain a stat chest radiograph** for placement (figure 7-36).



Figure 7-35: An introducer catheter



Figure 7-36: Plain PA chest x-ray showing a normal position of CVP catheter on the right side

- **Connection of the catheter:**

The cannulated vein is connected to either:

a- **A saline manometer** via an intravenous infusion set and a three-way tap. There should always be a **dependent loop of tubing** between the manometer and the patient to minimize the risk of air embolism if the CVP is below zero (figure 7-37). When the three-way tap is turned to connect the saline manometer to the vein, the saline meniscus should fall fairly rapidly and stabilize at the venous pressure. There are normally small respiratory fluctuations. The **absence of these respiratory swings** indicates that the catheter is situated peripherally or is blocked, and that measurement is not accepted. So, revising the position and flushing the catheter is required.

Presence of **marked cardiac pulsations** (and the recorded pressure is found to be higher than expected, usually $> 20 \text{ cm H}_2\text{O}$) indicates passage of the catheter into the right ventricle or pulmonary artery. It is simply corrected by withdrawing the catheter.

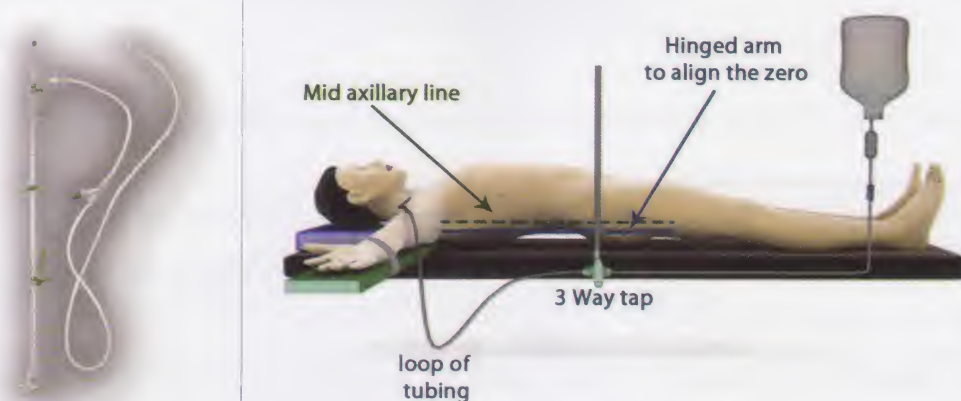


Figure 7-37: CVP measurement by a saline manometer

b- A line that is connected to a **diaphragm pressure transducer** (like the invasive blood pressure measurements). It gives a continuous recording and allows identification of the central venous pressure waveform.

Central Venous Access Sites

1- Veins of the Antecubital Fossa

Technique:

- Anatomical landmarks:

- The **basilic vein** lies at the **medial** side of the antecubital fossa and runs up the medial aspect of the arm. It is more preferred because it is slightly **larger** than the cephalic vein (8 mm vs. 6 mm in diameter), and it runs a **straighter** course up the arm.
- The **cephalic vein** lies at the **lateral** side of the antecubital fossa and runs up the lateral aspect of the arm (figure 7-38).

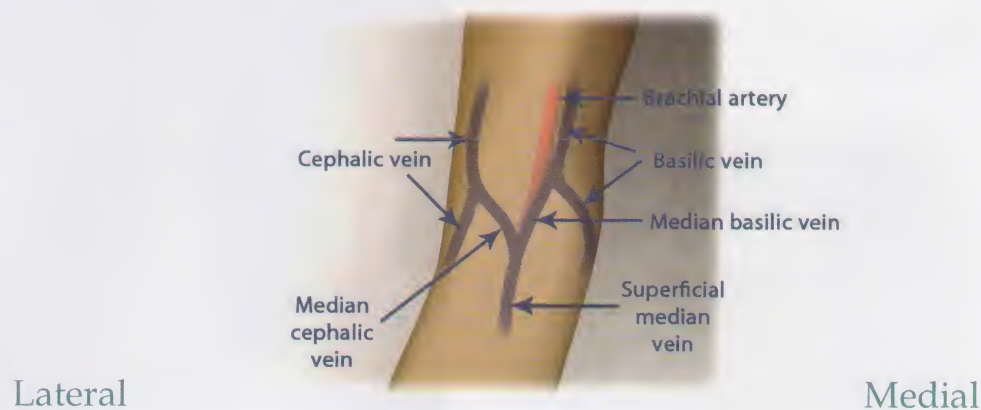


Figure 7-38: Antecubital veins

- **Peripherally inserted long central catheters** are needed. It should be advanced into the superior vena cava, just above the junction of the superior vena cava and right atrium. The position is detected either:

- Blindly, by a direct measurement of the distance from the antecubital fossa to the right third intercostal space over the skin.
- or - by the aid of fluoroscopy.

Advantages:

- The peripheral inserted catheters can be **left in place for 30 days** or longer without increased risk of catheter-related infections when compared with central venous catheters.
- There is **no risk of pneumothorax**.

Disadvantages:

- There is **more risk of thrombotic obstruction** because of their narrow bore.
- There is **more risk of mechanical phlebitis** because of their long length.

2- The Subclavian Vein

Technique:

- Patient position: Place the patient in Trendelenburg position, and place a towel roll between the scapulae. Turn the head opposite to the side of line placement.
- Anatomical landmarks: To locate the subclavian vein, identify the sternocleidomastoid muscle by palpation. This muscle has two heads; a medial sternal head inserted in the sternum and a lateral clavicular head inserted in the clavicle. The subclavian vein lies just underneath the clavicle at the point of insertion of the clavicular head in the clavicle (nearly between the lateral third and medial two-thirds of the clavicle). This area is marked. The vein can be entered at this point from below (infraclavicular) or above (supraclavicular) the clavicle.
- a- **Infraclavicular approach:** The probe needle should be inserted at a point below the clavicle just lateral to the marked area (as above). The bevel of the needle should be pointed upward (toward the ceiling) during insertion and the needle should be advanced just under the marked area of the clavicle (even touching the undersurface of the clavicle). The needle is directed medially towards the suprasternal notch and horizontally (parallel to the floor) and aspiration is performed while advancing. The needle will puncture the vein within a few centimeters of the surface. When the vein is entered, the bevel of the needle should be rotated to 3 o'clock so the guidewire threads in the direction of the superior vena cava.
- b- **Supraclavicular approach:** It is **easier** than the infraclavicular approach. The probe needle is inserted in the angle formed by the lateral margin of the sternocleidomastoid muscle and the clavicle. The needle is directed downward under the clavicle in the direction of the opposite nipple. The bevel of the needle should be upward then turned to 9 o'clock when the vein is entered so the guidewire threads in the direction of the superior vena cava. The subclavian vein is at 1 to 2 cm from the skin surface (more superficial in the supraclavicular approach) (figure 7-39).
- To confirm position of the catheters, the average distance from the cannulation site to the right atrium is 14.5 cm and 18.5 cm for right-sided and left-sided cannulations respectively. Therefore, to avoid placing catheters in the right side of the heart (which creates a risk of cardiac perforation), catheters used for subclavian (and internal jugular) vein cannulation should be no longer than 15 cm in length.

Advantages:

- It is a large vein with a diameter of 20 mm and remains patent despite hypovolemia due to the negativity of the thoracic pressure.
- It is not contraindicated in patients with coagulation disorders as the risk of major bleeding is uncommon.
- It is associated with a high degree of patient acceptance.

Disadvantages It is associated with a high risk of pneumothorax especially with inexperienced hands.

3- The Internal Jugular Vein

Technique:

- Patient position: Place the patient in **Trendelenburg position**, and have the patient **turn** his or her head 45 degrees to the direction opposite the site of catheter placement.
- Anatomical landmarks: The internal jugular vein is located under the sternocleidomastoid muscle in the neck and runs obliquely down the neck on a line from the pinna of the ear to the sternoclavicular joint. Turning the head to the opposite side will straighten the course of the vein. Near the base of the neck, the internal jugular vein lies just lateral to the carotid artery in the carotid sheath. The **right internal jugular vein is preferred** because the vessels run a **straighter course** to the right atrium. There are two approaches:
- a- **The anterior approach:** The operator must first identify a triangular area at the base of the neck created by the separation of the two heads of the sternocleidomastoid muscle. The carotid artery pulse is then palpated with the fingers of the left hand (for a right-sided approach), and the artery is retracted toward

the midline. The probe needle is then inserted at the apex of the triangle while aspirating with the bevel facing up and the needle is advanced toward the ipsilateral nipple, at a 45° angle with the skin surface. If the vein is not entered by a depth of 5 cm, the needle is drawn back and advanced again in a more lateral direction.

b- **The posterior approach:** The probe needle is inserted 1 cm superior to the point where the external jugular vein crosses the lateral edge of the sternocleidomastoid muscle. This point is usually at the level of the cricoid cartilage. The probe needle is advanced along the underbelly of the muscle in a direction pointing to the suprasternal notch or the contralateral nipple with the bevel directed at 3 o'clock position. The internal jugular vein should be encountered 5-6 cm from the skin surface (figure 7-39).

- Like the subclavian cannulation, catheters used for internal jugular vein cannulation should be no longer than 15 cm in length.

Advantages

- Some authors suggest that it is associated with less incidence of pneumothorax than subclavian vein cannulation, but this is denied by other authors.

Disadvantages

- The risk of pneumothorax is still high especially with inexperienced hands or due to protrusion of the cupola of the lung into the base of the neck as a result of the high tidal volumes used during mechanical ventilation.
- There is a high risk of carotid artery puncture. It is suggested by the return of pulsating bright red blood through the needle. If carotid artery is punctured by the probe needle, the needle should be removed and pressure applied to the site for at least 5 minutes (at least 10 minutes are required for patients with a coagulopathy). No further attempts should be made to cannulate the internal jugular vein on other side, to avoid puncture of both carotid arteries. If a catheter has been mistakenly placed in the carotid artery, do not remove the catheter and a vascular surgeon should be consulted.
- There is a risk of thoracic duct injury (on the left side).
- It is associated with poor patient acceptance due to limitation of neck mobility.

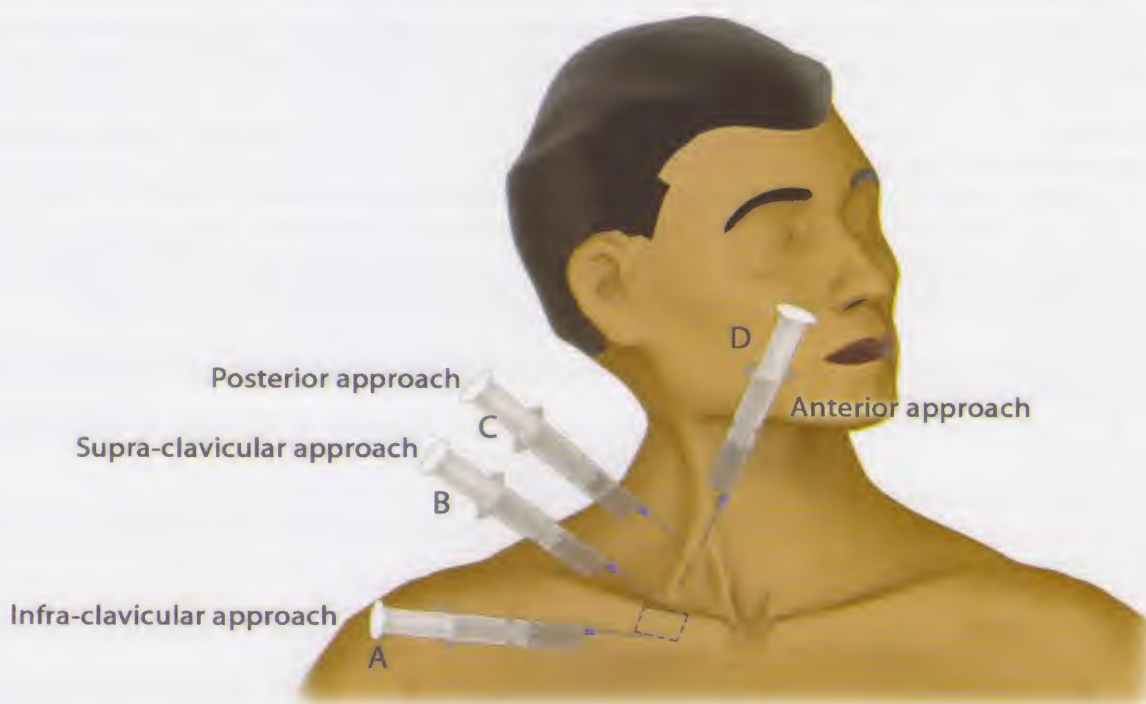


Figure 7-39: The points of insertion of subclavian (points A and B) and internal jugular vein (points C and D)

N.B.: **The External Jugular Vein**

Sometimes, the external jugular vein is cannulated by a central venous catheter where the catheter is threaded into the external jugular vein to reach the internal jugular vein (i.e., **externo-internal jugular vein cannulation**).

± The Femoral Vein

Technique

- Anatomical landmark: The femoral vein runs just medial to the femoral artery. The femoral vein is located by two methods:

- By palpating the femoral artery pulse just below the inguinal crease. The probe needle is inserted with bevel up 1-2 cm medial to the palpated pulse.
- By drawing an imaginary line from the anterior superior iliac spine to the pubic tubercle (if the femoral artery pulse is not palpable). This line is divided into 3 equal segments, where the femoral artery should be just underneath the junction between the middle and medial segments. The femoral vein lies 1-2 cm medial to this point (figure 7-40).

- The vein should be punctured at a depth of 2-4 cm from the skin.

Advantages

- It is the easiest central vein for cannulation because it is the largest.

Disadvantages

- There are higher rates of venous thrombosis and infection than other veins; therefore, femoral vein cannulation is not recommended as a primary site for central vein cannulation and if used, the catheter should be removed as soon as possible.
- There is a risk of femoral artery puncture.

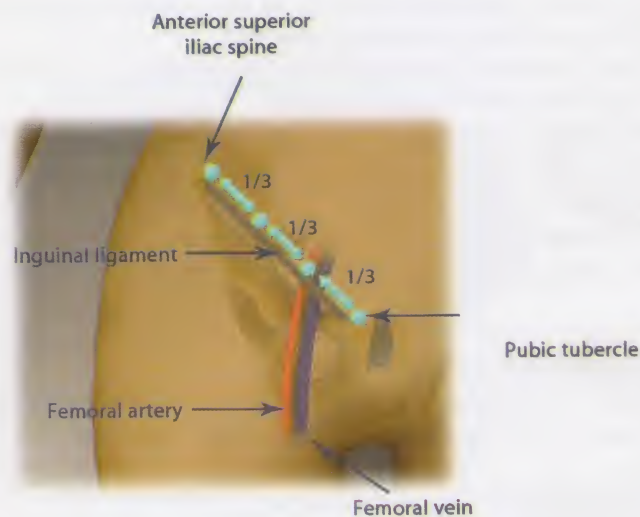


Figure 7-40: Cannulation of the femoral vein

- Recently, the use of **real-time ultrasonic probe** during catheter insertion is advisable especially in difficult cases to decrease complications such as arterial punctures and increase success rates.

Routine Catheter Care

The following measures can be used to decrease the complications associated with cannulation:

1- **Protective dressings:** Sterile gauze (or transparent semi-permeable dressings) is preferred to occlusive transparent polyurethane dressings as the latter enhance moisture, which provides a favorable medium for the growth of microorganisms.

2- **Antimicrobial ointment or gel:** Some authors discourage its usage due to possibility of development of antibiotic-resistant organisms.

3- **Replacement of the catheters:**

- The **peripheral venous catheters** should be replaced **every 3 to 4 days** (using a new venipuncture) to limit the risk of phlebitis. The arms are preferred to the legs because of the higher incidence of venous thrombosis in the legs.

- The **central venous catheters** should be replaced also **every 3 to 4 days** (using a new venipuncture or guidewire exchanger) to limit the risk of septicemia. Actually, catheter changes over a guidewire are no longer recommended as sterility cannot be assured. Guidewire exchange is only used, if new central venous access is difficult or the risk of insertion is high.

The routine central catheter replacements may be associated with mechanical and infectious complications and even it is not proved to decrease septicemia; therefore, **routine catheter exchange**

every 3-4 days is no longer recommended, but it is recommended to replace central venous catheters in the following conditions:

- Presence of purulent discharge from the catheter insertion site (erythema around the insertion site is not an absolute evidence of infection and not an indication for catheter replacement).
- A positive growth is obtained from a blood culture drawn through the catheter or from the tip of the previous catheter.
- Patients who are immunocompromised or have a prosthetic valve, or have severe sepsis.
- Catheters inserted without strict aseptic techniques in emergent situations where it should be replaced with new catheters aseptically.
- Femoral vein catheters placed more than 2 days.

4- Flushing of the catheters: Central venous catheters should be flushed at regular intervals with heparinized saline (with heparin concentration ranging from 10-1000 units/mL). It is not necessary to flush peripheral catheters, but arterial catheters should be flushed continuously at a rate of 3 mL/hour. Saline alone is as effective as heparinized saline for flushing venous catheters (not the arterial catheters), but 1.4% sodium citrate is a suitable alternative to heparinized saline for flushing arterial catheters.

Complications of Central Venous Cannulation:

According to the nearby structures of the selected vein and especially with a catheter-through a needle technique:

- 1- Trauma to **arteries** as: carotid, subclavian, femoral, or brachial causing bleeding.
- 2- Trauma to **nerves** as: brachial plexus, or stellate ganglion.
- 3- Trauma to the **lung and pleura** as: pneumothorax, hemothorax, or pleural effusion, so chest X-ray is essential after insertion especially with the subclavian.
- 4- Trauma to **the thoracic duct** as: chylothorax (with left internal jugular approach); therefore, cannulation of the right internal jugular vein is preferred.
- 5- Trauma to **the mediastinum** as: mediastinal effusion.
- 6- Trauma to **the heart** as: cardiac perforation, tamponade, dysrhythmias, or heart block.
- 7- Trauma to **the vein itself** as: extravasation, extravascular migration, hematoma, thrombosis, or thrombo-embolism.
- 8- **Emboli** as: air, catheter, or wire.
- 9- **Catheter knotting and catheter fracture.**
- 10- **Infection**, sepsis and endocarditis. The organisms most commonly involved with catheters are staphylococcus epidermidis (30%), staphylococcus aureus (8%), candida species (24%), and Gram-negative rods (18%).
- 11- Limitation of the movement in the site of insertion e.g., neck with internal or external jugular vein.
- 12- Catheter migration (figure 7-41).



Figure 7-41: Plain x-ray chest showing migration of an intravenous catheter to the head (arrows)

Most of these injuries are preventable by use of pressure waveform monitoring, chest radiography, or ultrasound-guided cannulation. The use of ultrasound-guided techniques decrease the failure rates and complications compared to standard techniques based on surface anatomy and palpation.

VI- Pulmonary Artery Catheterization (Pulmonary Artery Floatation Catheter or Swan-Ganz Catheter)

In 1970, Jeremy Swan, Ganz, and their colleagues described a catheter that could be floated into the pulmonary artery without the use of radiography or fluoroscopy.

Catheter Description:

It is a flow-directed catheter.

Material: polyvinyl chloride (PVC).

Length: 110 cm (marked at 10 cm intervals to facilitate insertion).

Outside diameter (size): 7 FG (double lumen).

7.5 FG (triple lumen).

Balloon: usually 1.5 mL capacity.

Lumens:

- The simplest form of the catheter has two channels (one for inflation of the balloon and the other for measurement of the pressure at the tip).
- More sophisticated versions have 4 or 5 lumens (figure 7-42).

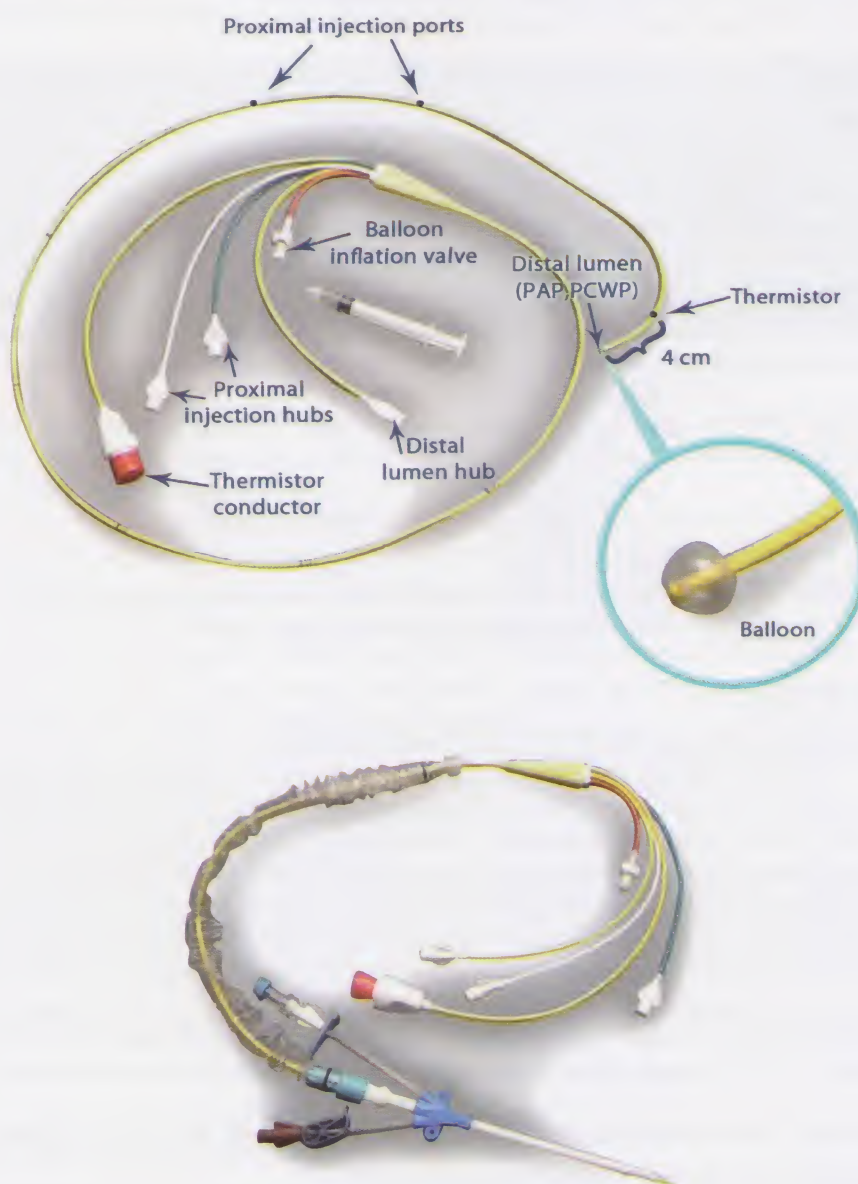


Figure 7-42: A 5-lumen pulmonary artery catheter (above) with the inflated balloon; and 5-lumen pulmonary artery catheter with a sleeve sheath and an introducer (down) (catheter contamination shield)

1- The Proximal Lumen (usually 2 in number):

It ends at **21-30 cm** from the tip of the catheter. Its opening should lie in the **right atrium** after final placement of the catheter.

It is used for • Central venous and right atrial pressure measurement.
• Fluid infusion.
• Cardiac output injections.

2- The Distal Lumen:

It ends at the catheter **tip**. Its opening should lie in a major branch of the pulmonary artery.

It is used for • Pulmonary artery pressure (**PAP**) measurement without wedging.
• Pulmonary capillary wedge pressure (**PCWP**) measurement with wedging.
• Aspiration of mixed venous blood samples (\bar{v}).

3- The Balloon Lumen:

It is used for inflation of the balloon by 1.5 mL air; the balloon surrounds the distal tip of the catheter. So, balloon inflation prevents the tip of the catheter to produce trauma.

4- The Thermistor Lumen:

It ends **4 cm** from the distal tip where a bead thermistor is mounted. It measures blood temperature. It is connected by a wire to a computer for cardiac output measurement.

Recent Advances in Pulmonary Artery Catheter

1- A **fiberoptic channel** for measuring **O₂ saturation** in pulmonary artery blood (mixed venous O₂ saturation).

2- A **pacing lead** for intracavitary pacing.

3- ECG electrodes for intracavitary ECG detection.

4- **Continuous cardiac output (CO) measurement:**

It is done by a **pulsed-thermodilution** technique. It is an injectless system which incorporates a thermal filament located 15-25 cm from the catheter tip. This thermal filament provides intermittent periods of heat, which are sensed by a distal rapidly responding thermistor. It allows measurement of the stroke volume of a single right ventricular contraction and **allows continuous cardiac output measurements**.

These accessories are present only in specially designed catheters (not in standard catheters) (figure 7-43).



Figure 7-43: Pulmonary artery catheter with continuous cardiac output measuring (left) and pacing (right) leads

Catheter Insertion:

- Before insertion: - The balloon is tested by inflation and deflation.
- Irrigation of the proximal and the distal lumens with heparinized saline is done.
- The catheter is passed through a large-bore introducer catheter (8.5 FG) situated in the subclavian or internal jugular vein via the Seldinger technique. When the catheter tip emerges from the introducer and is exposed to the flowing blood, the balloon is inflated with **1.5 mL of air (or saline)** and the catheter is advanced slowly with the balloon to protect the endocardium from injury by the catheter tip.
- Connect the distal port to a transducer that is zeroed to the patient's mid-axillary line. By recording the pressure waveforms on advancing the catheter, we can identify the catheter tip position (figure 7-44).

1- When the Catheter Tip is in the Superior Vena Cave (SVC) or Right Atrium: (nearly at **15 cm**).

The pressure in the SVC has a venous pattern and is called central venous pressure. It is equivalent to the right atrial pressure. If CVP tracing varies with respiration, this confirms the intra-thoracic position.

2- When the Catheter Tip is in the Right Ventricle: (nearly at **25 cm**)

When the catheter tip crosses the tricuspid valve and enters the right ventricle, a systolic pressure wave appears suddenly while the diastolic pressure remains the same.

During advancement, ECG monitoring is essential to detect arrhythmias as transient ventricular ectopy may occur from irritation of right atrial endocardium by the catheter which rarely needs intravenous lidocaine.

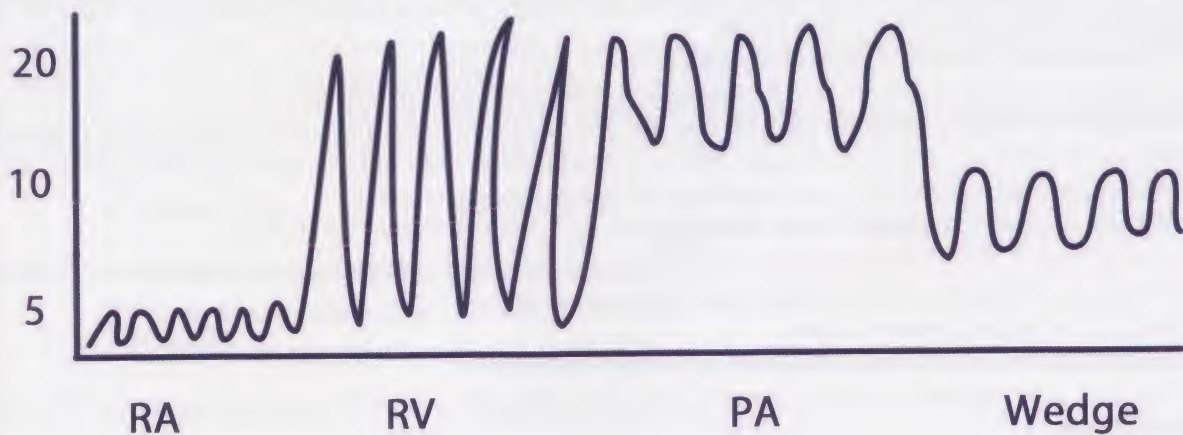


Figure 7-44: Pressure waveforms seen as the pulmonary artery catheter is advanced; right atrium (RA), right ventricle (RV), pulmonary artery (PA), and wedge pressure

Pressure	Normal Values	Remarks
- Right atrial pressure (RAP)	0-5 mm Hg	- As CVP value
- Right ventricular pressure (RVP)	15-30/0-4 mm Hg	- There is systole, but no diastole
- Pulmonary artery pressure (PAP)	15-30/6-12 mm Hg	- There are systole and diastole
- Pulmonary capillary wedge pressure (PCWP)	0-12 mm Hg	- Borderline is 13-17 and in heart failure is > 18 mm Hg
- Left atrial pressure (LAP)	0-12 mm Hg	- The same as PCWP.
- Left ventricular pressure (LVP)	120/0-8 mm Hg	- There is systole, but no diastole

3- When the Catheter Tip is in the Pulmonary Artery: (usually at 35-45 cm)

When the catheter tip crosses the pulmonary valve and enters the pulmonary artery, the diastolic pressure suddenly rises and a dicrotic notch (due to closure of pulmonary valve) appears on the waveform. This is the PAP waveform.

4- When the Catheter Tip is advanced Along the Pulmonary Artery for a Short Distance:

The systolic component of the pressure waveform will eventually disappear. This final pressure is called pulmonary capillary Wedge pressure (PCWP) or pulmonary artery occlusion pressure (PAOP). Wedging occurs usually when the balloon is in a branch of the pulmonary artery about 1 cm in diameter.

Once PCWP is obtained, the balloon is deflated and the PAP waveform should reappear, so the balloon is kept fully deflated and PAP is continuously monitored, except for brief periods of time to measure PCWP, thus minimizing the chance of pulmonary infarction.

Wedging before maximal balloon inflation indicates an over-wedged position, so the catheter should be withdrawn slightly (with the balloon deflated) as this may cause PA rupture.

The frequency of PCWP measurement should be minimal.

Confirmation of Correct Position is indicated by:

- 1- A decline in pressure as the catheter moves from the pulmonary artery into the "wedged" position.
- 2- Ability to aspirate blood from the distal port (eliminating the possibility of over-wedging).
- 3- Lateral chest X-ray to confirm position and to detect abnormal catheter migration to the vena cava anteriorly.
- 4- A decline in end-tidal CO₂ concentration with inflation of the balloon (produced by a rise in alveolar dead space).

Precautions:

- Never withdraw the catheter while the balloon is inflated.
- Never introduce the catheter while the balloon is deflated.
- Never leave wedging for a long time i.e., never to leave the balloon inflated for sustained periods as this may cause pulmonary artery rupture or pulmonary infarction.
- To avoid catheter knotting, the balloon should be deflated and the catheter should be withdrawn if the pressure changes do not occur at the expected distances.

- In patients receiving positive end expiratory pressure (PEEP), it is not recommended to stop PEEP to measure PCWP as its removal may cause:
 - a sudden decrease in arterial oxygenation.
 - a large increase in venous return causing acute hemodynamic instability.
 - The effect of airway pressure on PAP tracing: Fluctuation in intra-thoracic pressure due to respiratory pattern and mode of ventilation causes difficult interpretation of PCWP. To decrease these effects, use an oscilloscope to interpret PCWP and reading is done at the end-expiration.
 - Natural resonance frequency and damping can occur (as in arterial cannulation).
- In Difficult Cases of Insertion:** e.g., low cardiac output, pulmonary hypertension or congenital heart disease, floatation of the catheter may be enhanced by:
- Having the patient inhale deeply.
 - Positioning the patient with a head up or in right lateral tilt.
 - Injecting iced saline via the proximal lumen to stiffen the catheter (but this increases the risk of perforation).
 - Giving small dose of an inotropic agent to increase cardiac output e.g., Ca^{++} .

Indications:

1- Cardiac Causes: when there is dissociation between left and right sided hemodynamics i.e., between LAP (PCWP) and RAP (CVP) which occurs in:

- Poor left ventricular function (i.e., failure) with: ejection fraction < 0.5 , left ventricular end diastolic pressure (LVEDP) > 15 mmHg, cardiac index < 2 L/min/m², with/without pulmonary edema e.g., in cardiomyopathy, pericardial tamponade, and severe toxemia of pregnancy.

In a patient with left heart disease excessive intravenous transfusion can cause pulmonary edema before the warning sign of a high CVP is seen.

On the other hand, in a patient with lung disease, right sided heart failure may occur with a high CVP without left sided heart failure.

- Severe valvular heart diseases.
- Severe coronary artery disease or recent myocardial infarction (< 6 months duration).
- Pulmonary edema of any cause.
- Ventricular septal defects as O_2 saturation of the right ventricle is $>$ right atrium.

N.B.: Both CVP and PCWP are called the filling pressures of the right and left ventricles respectively. The normal heart fills to a greater extent and automatically increases its output even in the absence of autonomic innervation. This is called **Starling's law of the heart**.

When the heart is normal, there is a little difference between right and left heart filling pressures. However, when cardiac disease is present, there may be a marked disparity between right and left atrial pressures.

2- Differentiation between Different Types of Shocks:

	Hypovolemic Shock	Cardiogenic Shock or Heart Failure		Hyperdynamic Shock
CVP	Low	High		Low
Cardiac index	Low	Low		High
Systemic vascular resistance	High	High		Low
		Cardiogenic shock Low O_2 uptake ($\dot{\text{V}}\text{O}_2$) with inadequate tissue oxygenation	Heart failure Normal O_2 uptake ($\dot{\text{V}}\text{O}_2$) with adequate tissue oxygenation	

3- Pulmonary Disease:

- Acute respiratory failure as pulmonary emboli, acute respiratory distress syndrome (ARDS), or pulmonary hypertension.
- Severe chronic obstructive pulmonary diseases (COPD) and cor pulmonale.

Complex Fluid Management:

This complex management is confronted in cases such as those with major fluid shift and/or loss e.g., placental abruption, burns, polytrauma and acute renal failure. This is achieved by **7-3 rule** which is used as a guide for fluid management (figure 7-45).

If the ventricles become over-filled, large changes in pressure will occur for small changes in volume due to decreased compliance.

If initial PCWP	give fluids as
< 10 mmHg	200 cc in 10 minutes.
10–15 mmHg	100 cc in 10 minutes.
> 15 mmHg	50 cc in 10 minutes.
If the response is	the therapy is
PCWP \uparrow > 7 mmHg	Stop fluids.
PCWP \uparrow 3 – 7 mmHg	Wait another 10 minutes, if still > 3 mmHg so, stop fluids.
PCWP \uparrow < 3 mmHg	Continue fluids.

Figure 7-45: 7-3 rule

Specific Surgical Procedures:

- Coronary artery bypass grafting surgery (CABG).
- Valve replacement.
- Pericardiectomy.
- Aortic cross clamping (e.g., during aortic aneurysm repair).
- Sitting craniotomy to detect air embolism.
- Portal systemic shunts (e.g., during liver transplantation).

With Special Therapies:

- Inotropic therapy.
- Intra-aortic balloon pump.
- Mechanical ventilation with a high PEEP.

N.B.: The initial enthusiasm for the use of Swan-Ganz catheter is now being tempered by the frequent incidence of complications and the resultant morbidity and mortality.

Contraindications (relative):**Cardiac Causes:**

- Tricuspid or pulmonary valve disease/replacement.
- Recent pacemaker insertion.
- Ventricular arrhythmias.
- Left bundle branch block as it may cause a complete heart block; therefore, a catheter with a pacing capability is preferred.
- Wolf-Parkinson-White syndrome or Ebstein's anomaly.

Catheter Causes:

- Coagulopathy as the catheter may cause bleeding.
- Hypercoagulopathy as the catheter acts as a nidus for thrombus formation.
- Septic patients as the catheter acts as a nidus for infection.

Value:**A- Measurement of Hemodynamic Parameters:****Central Venous Pressure (CVP):**

It is the pressure recorded from the proximal port of the catheter situated in the right atrium.

RAP should be equivalent to right ventricular end-diastolic pressure (RVEDP), unless there is an obstruction between the atrium and the ventricle i.e., $CVP = RVEDP$, and it can indicate the left side except if there is a dissociation between the left and the right side (as above).

Pulmonary Artery Pressure (PAP):

It is the pressure recorded from the distal port of the catheter, situated in the distal part of the pulmonary artery while the balloon is deflated.

3- Pulmonary Artery Occlusion Pressure (PAOP), or Pulmonary Capillary Wedge Pressure (PCWP):

It is the pressure recorded from the distal port of the catheter when the balloon is lodged in the distal part of the pulmonary artery while it is inflated.

This pressure is considered the left sided cardiac filling pressure and is considered equivalent to the left atrial pressure or left ventricular end diastolic pressure (LVEDP)

i.e., $PCWP = LAP = LVEDP \rightarrow LVED$ volume, but PCWP (estimated preload) does not equal LVEDP (actual preload) in the following conditions:

PCWP is < LVEDP in:

- 1- Decreased left ventricular compliance (stiff ventricle or LVEDP > 25 mm Hg).
- 2- Aortic insufficiency.

PCWP is > LVEDP in;

- 1- Mitral stenosis.
- 2- Left atrial myxoma.
- 3- Pulmonary venous obstruction.
- 4- Elevated alveolar pressure (high airway pressure) and application of PEEP.

PCWP also can assess myocardial ischemia intraoperatively as PCWP increases and its tracing ("a" and "v" waves) usually change early, due to changed ventricular compliance and possible papillary muscle dysfunction as a result of ischemia. It is not as sensitive or specific as trans-esophageal echocardiography.

4- Cardiac Output (CO):

Cardiac output can be measured by a **thermodilution** technique by the thermistor located 4 cm from the catheter tip.

B- Derived (Calculated) Hemodynamic Parameters: (figure 7-46)

Variables	Formula	Normal Value	Units
1- Cardiac Index (CI)	$\frac{CO (L/min)}{Body\ surface\ area (m^2)}$	2.2 - 4.2	L / min / m ²
2- Stroke Volume (SV)	$\frac{CO (L/min) \times 1000}{Heart\ rate (beats/min)}$	60 - 90	mL / beat
3- Stroke Volume Index (SVI)	$\frac{Stroke\ volume (mL/beat)}{Body\ surface\ area (m^2)}$	40 - 60	mL / beat / m ²
4- Left Ventricular Stroke Work Index (LVSWI)	$0.0136 (MAP - PCWP) \times SVI$ - It represents the work performed by the left ventricle to eject the stroke volume into the aorta. - The factor 0.0136 corrects the pressure and the volume to units of work.	40 - 60	g - m / beat / m ² g - m = gram-meter
5- Right Ventricular Stroke Work Index (RVSWI)	$0.0136 (PAP - CVP) \times SVI$	5 - 10	g - m / beat / m ²
6- Systemic Vascular Resistance (total peripheral resistance i.e., venous and arterial)	$\frac{(MAP - CVP) \times 80}{CO (L/min)}$ The factor 80 converts pressure (mm Hg) and volume to dynes.sec.cm ⁻⁵	900 - 1500	Dyne.sec.cm ⁻⁵
7- Systemic Vascular Resistance Index	$\frac{(MAP - CVP) \times 80}{CI}$	1600 - 2400	Dyne.sec.cm ⁻⁵ .m ²
8- Pulmonary Vascular Resistance	$\frac{(PAP - PCWP) \times 80}{CO (L/min)}$	50 - 150	Dyne.sec.cm ⁻⁵
9- Pulmonary Vascular Resistance Index	$\frac{(PAP - PCWP) \times 80}{CI}$	200 - 400	Dyne.sec.cm ⁻⁵ .m ²

N.B.: Ejection Fraction (EF) = ratio of stroke volume to end-diastolic volume.

$$= \frac{EDV - ESV}{EDV}$$

$$= \frac{SV}{EDV}$$

Left ventricular ejection fraction = 0.56 - 0.75 (56-75%).

Right ventricular ejection fraction = 0.46 - 0.50 (46 - 50%).

N.B.: Pulmonary vascular resistance = $\frac{\text{PAP} - \text{PCWP}}{\text{CO}} = 1 \text{ wood unit.}$

1 wood unit = 1 mm Hg/L/min = 80 dyne.second.cm⁻⁵

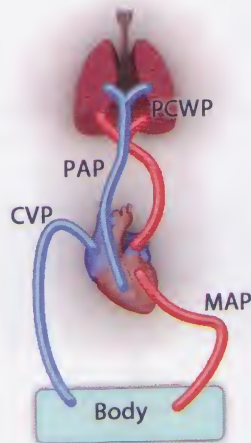


Figure 7-46: Different pressures associated with the pulmonary artery catheter

C- Other Variables with Sampling of Mixed Venous Blood:

The following abbreviations are used:

CaO₂ = Arterial O₂ content.

C \bar{v} O₂ = mixed venous O₂ content.

SaO₂ = Arterial O₂ saturation.

CcO₂ = O₂ content in the end pulmonary capillary.

CO = Cardiac output.

Hb = Hemoglobin.

• = The dot above the letters indicates the volume or amount per unit time.

1- O₂ Delivery ($\dot{V}O_2$) = O₂ flux

It is the amount of O₂ delivered to the capillaries/minute.

$$\begin{aligned}\dot{V}O_2 &= \text{CO} \times \text{CaO}_2 \quad \text{mL/min} \\ &= \text{CO} \times (\text{chemically combined with Hb} + \text{physically dissolved in plasma}) \\ &= \text{CO} \times ([\text{Hb g/dL} \times 1.38 \times \text{SaO}_2 \%] + [0.003 \times \text{PaO}_2 \text{ mm Hg}]) \\ &= \text{CO} \times ([15 \times 1.38 \times 97/100] + [0.003 \times 95]) \\ &= \text{CO} \times 20.6 \text{ mL/dL} \\ &\text{as } [0.003 \times \text{PaO}_2 \text{ mm Hg}] \text{ is of little value, it has a little effect.}\end{aligned}$$

$$\begin{aligned}\text{So, } \dot{V}O_2 &= \text{CO} \times \text{Hb g/dL} \times 1.38 \times \text{SaO}_2 \\ &= 850\text{-}1050 \text{ mL/min}\end{aligned}$$

N.B.:

- 1.38 is the **Hufner factor** that means that each one gram % of Hb, when it is 100 % saturated, can carry 1.38 mL of O₂.
- 0.003 is the **solubility coefficient** of O₂ in water at 37 °C i.e., at partial pressure of O₂ equal to one, the amount of O₂ that dissolves in plasma is 0.003 mL.
- O₂ content in arterial blood (CaO₂) = 20.6 mL/dL.

2- O₂ Uptake ($\dot{V}O_2$): by tissue = O₂ consumption (Fick's equation) (figure 7-47).

It is the amount of O₂ taken up from the capillaries/minute.

$$\begin{aligned}\dot{V}O_2 &= \text{CO} \times (\text{CaO}_2 - \text{C}\bar{\text{v}}\text{O}_2) \quad \text{mL/min} \\ &= \text{CO} \times \text{Hb} \times 1.38 \times (\text{SaO}_2 - \text{S}\bar{\text{v}}\text{O}_2) \\ &= 250 \text{ mL/min}\end{aligned}$$

N.B.: • During exercise $\dot{V}O_2$ (maximum) occurs. Healthy individuals can increase both CO and the difference (SaO₂-S \bar{v} O₂) by a factor of 3

$$\dot{V}_{O_2} (\text{maximum}) = \frac{5000}{100} \text{ mL/min} \times 15 \text{ g\%} \times 1.38 (98/100-31/100) \times 3$$

$$= 2080 \text{ mL/min.}$$

i.e., \dot{V}_{O_2} can be increased up to 9 folds.

- O_2 content in mixed venous blood ($C\bar{v}O_2$) = 15.6 mL/dL.

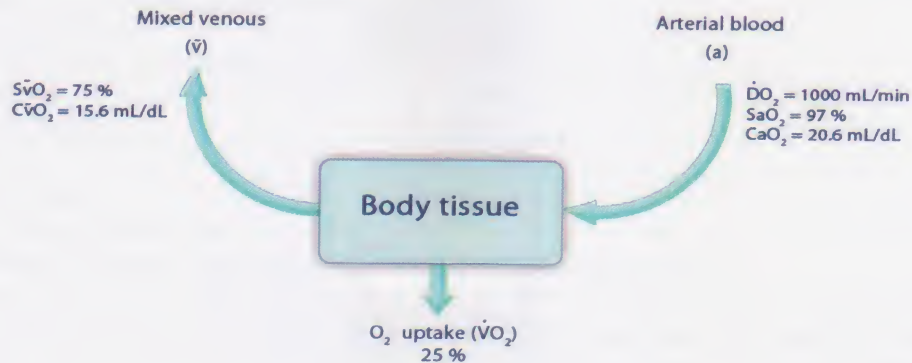


Figure 7-47: O_2 uptake

3- O_2 Extraction Ratio (O_2ER):

It is the ratio of O_2 uptake to O_2 delivery rate.

$$O_2ER = \dot{V}_{O_2} / \dot{D}O_2$$

$$= 20 - 30\% \text{ Normally.}$$

N.B.: A decrease in $\dot{D}O_2$ is associated with an increase in O_2ER , until the latter reaches its maximum (the maximal O_2ER is 50%). A further decrease in $\dot{D}O_2$ is accompanied by a decrease in \dot{V}_{O_2} ; therefore, \dot{V}_{O_2} becomes supply dependant causing a decrease in ATP. This is called **dysoxia** (i.e., hypovolemic shock).

The $\dot{D}O_2$ at which \dot{V}_{O_2} becomes supply dependant is called the **critical O_2 delivery** ($\dot{D}O_{2c}$).

4- Mixed Venous O_2 Saturation ($S\bar{v}O_2$):

It is the amount of O_2 combined to Hb in the pulmonary artery.

Normal value = 75%

$$S\bar{v}O_2 = SaO_2 - \frac{\dot{V}_{O_2}}{CO \times Hb \times 1.38} \quad \text{as derived from Fick's equation.}$$

So, from the equation $S\bar{v}O_2$ is directly proportionate to SaO_2 , CO, and Hb

& inversely proportionate to \dot{V}_{O_2} .

So, **Decreased $S\bar{v}O_2$ indicates:**

- Increased O_2 consumption or tissue uptake i.e., increased \dot{V}_{O_2} .
- A decrease in one of the components of O_2 delivery e.g., - decreased SaO_2 as hypoxemia.
- decreased cardiac output.
- decreased Hb % as anemia.

Increased $S\bar{v}O_2$ indicates:

- Decreased O_2 consumption as - hypothermia,
or - histotoxic hypoxia (carbon monoxide or cyanide poisoning).
- An increase in one of the components of O_2 delivery e.g.,
- Increased SaO_2 as hyperoxia, sampling with catheter wedged or rapid aspiration of pulmonary artery blood sample although the catheter is not wedged.
- Increased cardiac output as sepsis, porto-caval shunt, arterio-venous fistula, Paget's disease of the bone, or increased dose of inotropic drugs.
- Increased Hb % as polycythemia.

N.B.: **Dual Oximetry:**

It is the simultaneous measurement of:

- Arterial O_2 saturation (SaO_2) by a pulse oximeter.

and • Mixed venous O_2 saturation ($\bar{S}O_2$) by a pulmonary artery catheter.

$$\dot{V}O_2 = CO \times Hb \times 1.38 \times (SaO_2 - \bar{S}O_2)$$

$$So, \quad SaO_2 - \bar{S}O_2 = \frac{\dot{V}_{O_2}}{CO \times Hb \times 1.38}$$

So, $SaO_2 - \bar{S}O_2$ is: - directly proportionate to $\dot{V}O_2$ (O_2 consumption, tissue O_2 uptake or metabolic rate)
and - inversely proportionate to CO and Hb%.

Therefore,

$SaO_2 - \bar{S}O_2$ range	Interpretation
20 - 30 %	Normal
30 - 50 %	Hyper-metabolic rate, anemia or decreased CO
> 50 - 60%	High risk dysoxia and blood transfusion trigger point

↳ Intrapulmonary Shunt Equation:

$$= \frac{C\bar{C}O_2 - CaO_2}{C\bar{C}O_2 - \bar{C}O_2} \quad \text{or} \quad = \frac{1 - SaO_2}{\bar{S}O_2}$$

$C\bar{C}O_2$ is measured by a pulmonary artery catheter during wedging.

Complications:

a) Complications of Central Venous Cannulation:

It is discussed in central venous catheterization (as before).

b) Complications Specific to the Swan-Ganz Catheter:

1- The heart:

- Pulmonary and tricuspid valve trauma.
- Tricuspid incompetence.
- Ventricular arrhythmias.
- Complete heart block due to occurrence of right bundle branch block in a patient with left bundle branch block.

2- The lungs:

- Pulmonary infarction (due to continuous wedging).
- Pulmonary hemorrhage especially in an anticoagulated patient.
- Rupture of pulmonary artery especially in elderly females or with pulmonary hypertension.

3- The balloon and catheter:

- Rupture.
- Coiling in the right ventricle with the possibility of knotting.
- Transient hypotension and hypoxemia with balloon inflation.

Due to these complications, some clinicians do not prefer to use it.

VII- Measurement of Cardiac Output (CO)

Indications:

The indications are discussed in pulmonary artery catheterization.

Contraindications:

The contraindications of pulmonary artery catheterization are discussed above.

Value:

Many indices are derived from cardiac output "see pulmonary artery catheterization".

Technique:

They include:

A- Invasive techniques:

- 1- Fick principle technique (by oxygen or carbon dioxide).
- 2- Indicator dilution technique:
 - Single injection indicator dilution.
 - Continuous infusion indicator dilution.
- 3- Thermal indicator dilution (thermodilution) technique.

- 4- Pulse contour analysis (arterial waveform analysis):
 - Pulse induced continuous cardiac output monitor (PiCCO).
 - Lithium dilution cardiac output (LiDCO).
 - FloTrac/Vigileo.
- 5- Arterial pulse pressure variation.

B- Non-invasive techniques:

- 1- Doppler ultrasonography.
- 2- Thoracic electrical bio-impedance.
- 3- Differential Fick principle or NICO® system.
- 4- Magnetic resonance imaging.
- 5- The Bradley method.

A- Invasive Techniques

1- Fick's Principle Technique:

It is the standard method of measurement of cardiac output to which all the other methods are judged.

Idea:

As above, cardiac output (\dot{Q}_t) or pulmonary blood flow may be calculated by using either: oxygen or carbon dioxide.

a) Oxygen:

$$\text{As } \dot{V}_{O_2} = \dot{Q}_t \times (CaO_2 - C\bar{v}O_2)$$

$$\text{So, } \dot{Q}_t = \frac{\dot{V}_{O_2}}{CaO_2 - C\bar{v}O_2} = \frac{250 \text{ mL/min}}{20.6 \text{ mL/d} - 15.6 \text{ mL/d}} = 5 \text{ liter/min}$$

Where:

\dot{Q}_t = Blood flow = Cardiac output.

\dot{V}_{O_2} = oxygen consumption which is measured by a spirometer filled with oxygen using a metabolic cart, where the amount of oxygen consumed is calculated in mL/min.

CaO_2 = oxygen content of arterial blood, which is obtained directly from an arterial blood sample.

$C\bar{v}O_2$ = oxygen content of mixed venous blood which is obtained from a pulmonary artery catheter.

b) Carbon Dioxide Excretion can be used using the same Fick's principle where the denominator is $C\bar{v}CO_2 - CaCO_2$ since the gas is excreted instead of being taken up.

$$\dot{Q}_t = \frac{\dot{V}_{CO_2}}{C\bar{v}CO_2 - CaCO_2}$$

Where:

\dot{V}_{CO_2} = CO_2 clearance or washout from the lungs.

$CaCO_2$ = arterial CO_2 content which is obtained by using the end-tidal CO_2 in a steady state.

$C\bar{v}CO_2$ = mixed venous CO_2 content which is obtained from a pulmonary artery catheter.

2- Indicator Dilution Technique:

A) Single Injection Indicator Dilution:

Idea:

An indicator is injected into the vena cava, right heart, or preferably the pulmonary artery. The concentration of the indicator reaching the systemic side of the circulation is then plotted against time (figure 7-48).

The indicator used may be:

- **Indocyanine green dye:** It is the most popular and has the following advantages:
 - Non-toxic.
 - With relatively short half life time.
 - Has a peak spectral absorption at 800 nm, which is the wavelength at which the absorption of oxygenated and reduced hemoglobin is identical. The measurement is therefore not affected by changes in arterial saturation.
- Radioactive human serum albumin.
- Chromium-labeled red cells.

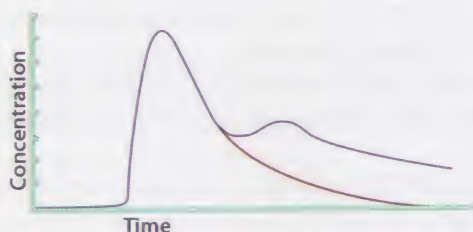


Figure 7-48: Single injection indicator dilution curve

The concentration of the dye or isotope in the systemic circulation is obtained by one of the following methods:

- In the original Stewart-Hamilton method, a continuous stream of blood from a peripheral artery is allowed to flow into a series of 30 small tubes which are sequentially moved by a rotating disc. Each blood sample is then analyzed separately and the curve is plotted by hand.
- Nowadays, the dye concentration is recorded by a densitometer (a spectrophotometer) where the arterial blood is sampled at a continuous rate of about 30 ml/min. Recently, a fiberoptic densitometer has been inserted into a catheter.
- For radioactive measurements, a scintillation detector is used to record the radioactivity in the blood samples.

The area under the curve is measured by either:

- A planimeter (an instrument for manual measurement of the area under the curve).
- A microprocessor.

For example:

If the amount of the indicator injected is 5 mg and the duration of the curve is 30 seconds, the mean concentration of the indicator on the systemic side is 2 mg/L (calculated from the area under the curve divided by the duration of the curve).

Therefore, the volume of the blood in 30 seconds can be calculated as follows:

$$\frac{\text{Amount of indicator given (mg)}}{\text{Mean concentration of indicator calculated (mg/L)}} = \frac{5 \text{ mg}}{2 \text{ mg/L}} = 2.5 \text{ L of blood during the 30 sec.}$$

As cardiac output (CO) during 30 sec is 2.5 L

$$\text{Therefore, CO during 60 sec} = \frac{60 \text{ sec} \times 2.5 \text{ L}}{30 \text{ sec}} = 5 \text{ L/min.}$$

$$\text{The general formula of CO (L/min)} = \frac{60 \text{ (sec)} \times \text{indicator dose (mg)}}{\text{Duration of curve (sec)} \times \text{mean concentration (mg/L)}}$$

Disadvantages:

This method has the problem of the recirculation of the indicator, which occurs before the down-slope of the curve is complete i.e., the curve rises to the peak and then declines to rise again because the indicator e.g., indocyanine green is not completely metabolized or cleared during a single passage through the liver. This problem is eliminated by assuming an exponential clearance of the indicator and predicting the tail of the curve from the initial down-slope recorded before recirculation occurs i.e., extrapolation of the descending limb of the curve is done.

Continuous Infusion Indicator Dilution:

A substance is injected into one part of the circulation at a constant rate and its concentration is sampled elsewhere. From the dilution of the injected substance, it is possible to calculate the flow rate provided recirculation does not occur.

$$\text{Cardiac output} = \frac{\text{rate of infusion of indicator}}{\text{concentration of the indicator in blood}}$$

Thermal Indicator Dilution (Thermodilution) Technique:

This technique is the one used now in anesthesia and intensive care units by using the pulmonary artery catheter.

Idea:

The principle of this method is similar to other indicator dilution techniques, but the injection and sampling are performed on the right side of the heart.

Ten mL normal saline or 5% dextrose solution at below body temperature (either room temperature or iced at 4 °C) are injected into the right atrium and the temperature change of blood is recorded by a thermistor in the pulmonary artery.

The thermo-dilution curve which results is similar in shape to the dye dilution curve, but there is **no recirculation** (figure 7-49).

$$CO = \frac{\text{Temperature difference between the injectate and blood} \times \text{density} \times \text{specific heat} \times \text{volume of injectate}}{\text{Area under temperature time curve} \times \text{density} \times \text{specific heat of blood}}$$

Nowadays, microprocessors are used to draw the curve and calculate the CO.

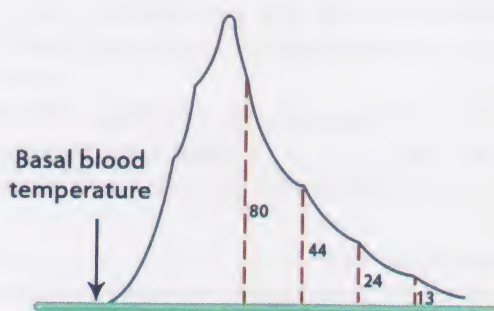
The degree of change is inversely proportionate to the cardiac output:

- If the temperature change is minimal, there is high blood flow,
- and • If the temperature change is maximal, there is low blood flow.

Accurate measurements depend upon:

- Rapid and smooth injection, and a precisely known injectate temperature and volume.
- Correct entry of the calibration factors for the specific type of pulmonary artery catheter and injectate into the computer.
- Avoidance of measurement during electrocautery.
- Avoidance of measurement in tricuspid regurgitation and cardiac shunts as they invalidate results because only right ventricular output is actually being measured.
- Proper transducer zeroing.

Recently, continuous cardiac output assessment (beat to beat) can be done (see before).



Mean residual fraction $RF1 = 44/80 = 0.55$.

$RF2 = 24/44 = 0.55$.

$RF3 = 13/24 = 0.54$.

Ejection fraction (EF) = $1 - RF = 0.45$.

RV stroke volume = cardiac output / heart rate

RV end diastolic volume = RV stroke volume / RV EF

RV end - systolic volume =

RV end-diastolic volume - RV stroke volume

Figure 7-49: Thermo-dilution curve

Advantages:

- 1- The indicator is cheap, non-toxic and repeated measurements may be made without much alteration in the baseline (with dyes or isotopes the background level builds up progressively, thus limiting the number of measurements which can be performed).
- 2- Arterial puncture and blood withdrawal is not necessary.
- 3- Absence of recirculation gives more accurate results, especially during low cardiac output states.

Disadvantages:

- 1- This technique requires correct placement of a special catheter (pulmonary artery catheter) which is expensive.
- 2- The pulmonary arterial flow varies much more with mechanical ventilation than the systemic flow.

3- The temperature of blood in the pulmonary artery fluctuates with respiration. Injection during inspiration may give very different results from those obtained with injection during expiration.

4- **Pulse Contour Analysis (Arterial Waveform Analysis):**

As the rate at which blood flows from arteries to veins is proportional to the rate of fall of blood pressure, the analysis of the contour of arterial pulse wave obtained non-invasively by Finapres or invasively by arterial cannula can be used for cardiac output monitoring.

Left ventricular stroke volume can be estimated from **the area under the systolic part of the arterial pressure waveform**. This technique can be affected by changes in systemic vascular resistance; therefore, intermittent recalibration by thermo-dilution is mandatory.

Pulse Contour Devices are devices that use computer-driven algorithms to translate the arterial pressure tracing into cardiac output and other variables. These devices include: PiCCO, LiDCO, and FloTrac/Vigileo.

4- **Pulse Induced Continuous Cardiac Output Monitor (PiCCO):**

Physical Principles:

It involves a combination of both the arterial **pulse contour analysis** and **trans-pulmonary thermo-dilution**.

4- **Pulse contour analysis: the stroke volume** equals the integral of the area under the systolic portion of the arterial pressure waveform divided by the impedance of the aorta (Z) (figure 7-50) or mathematically stated:

$$SV = \frac{a}{Z} = \frac{\int dP/dt}{Z}$$

Where: SV = stroke volume

Z = impedance of the aorta

a = area under the systolic portion of the curve

dP = delta pressure

dt = delta time

This physiological principle is similar to $SV = \frac{\text{Pulse pressure}}{\text{Arterial compliance}}$

Therefore, left ventricular cardiac output = stroke volume x heart rate.

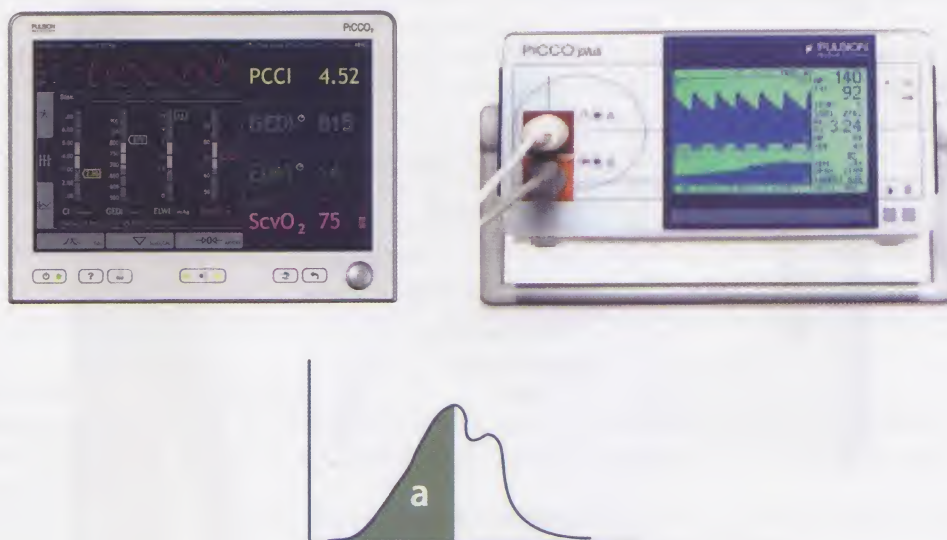


Figure 7-50: The PiCCO device (above left), PiCCO plus (above right) and stroke volume calculation from the arterial pressure waveform (down)

b- Trans-pulmonary thermodilution: Most of the diminution in temperature of the injectate occurs within the pulmonary vascular bed.

Technique:

- The PiCCO catheter relies on the insertion of:

- a **proprietary arterial line with a temperature sensor at the tip** that must be placed in the femoral or axillary artery by Seldinger technique, and
- a **standard central venous line** with its tip in the superior vena cava. A **CeVOX probe** is usually used and inserted via existing standard central venous catheter. It allows continuous fiberoptic central venous oxymetry (ScvO₂). CeVOX probes are available in lengths from 30-48 cm. The inserted probe has to exceed the tip of the catheter by 2.5 ± 0.5 cm (figure 7-51).
There is no need for pulmonary artery catheterization.



Figure 7-51: PiCCO catheter (left) and CeVOX probe (right)

- These two catheters are used to determine cardiac output by means of the injection of a cold fluid bolus ($< 8^{\circ}\text{C}$) or fluid bolus at room temperature ($< 24^{\circ}\text{C}$) into the superior vena cava and monitoring of the temperature change in the artery; this is done via a **modified Stewart-Hamilton equation** and the resultant value is termed the **"trans-pulmonary thermodilution cardiac output"**. After calibration, the device reports cardiac output and stroke volume (SV) continuously (figure 7-52). From the analysis of the pulse contour, SV variance is also reported. Other parameters can be measured (see below).

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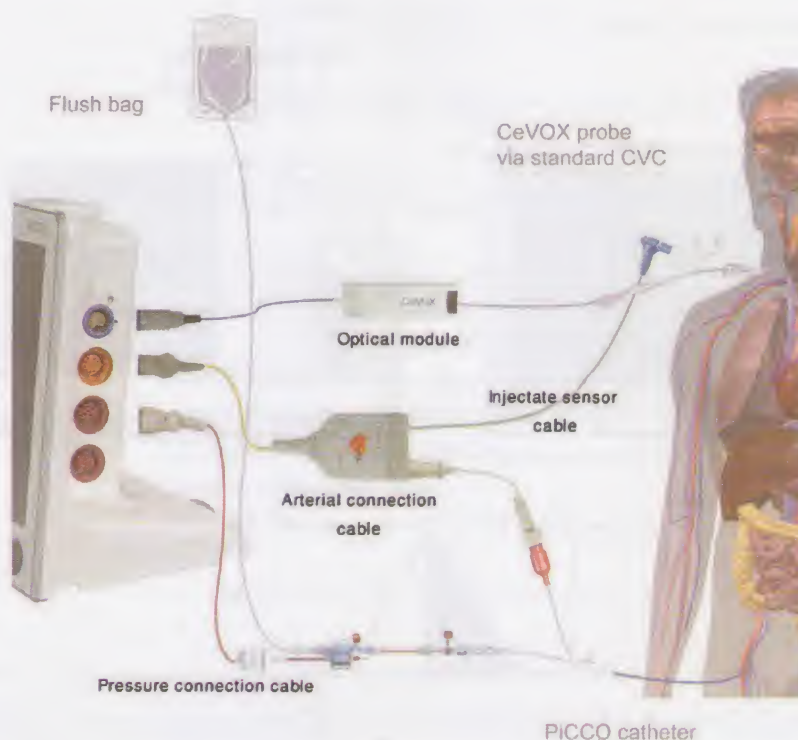


Figure 7-52: PiCCO setup

Advantages:

- There is no need for pulmonary artery catheterization.
- It can be applicable in small children.
- It allows beat-to-beat continuous measurement of cardiac output.
- It allows measurement of many parameters.

Parameters measured by the PiCCO:**a- Parameters assessing the flow:**

- **Cardiac output (CO).**
- **Cardiac index (CI):** Its normal value is 3-5 L/min/m².
- **Stroke volume (SV).**
- **Stroke volume index (SVI):** Its normal value is 40-60 mL/m².
- **Pulse contour cardiac output (PCCO).**
- **Pulse contour cardiac index (PCCI).**

b- Parameters assessing preload: i.e., the volume of blood in the heart available to be pumped.

- **Global end-diastolic volume (GEDV);** it is the volume of blood in the 4 chambers of the heart.
- **Global end-diastolic volume index (GEDI);** it is the GEDV indexed to predicted body surface area. Its normal value is 680-800 mL/m².
- **Intrathoracic blood volume (ITBV);** it is the volume of the 4 chambers of the heart plus the volume in the pulmonary vessels.
- **Intrathoracic blood volume index (ITBI);** it is ITBI indexed to predicted body surface area. Its normal value is 850-1000 mL/m².

The intrathoracic blood volume and global end-diastolic volume are more sensitive and specific to cardiac preload than the standard cardiac filling pressures, central venous and pulmonary capillary wedge pressures.

c- Parameters assessing volume responsiveness: i.e., the reaction of cardiac output to an increase in preload.

- **Stroke volume variation (SVV);** it is the changes in stroke volume over the respiratory cycle i.e., it assesses the sensitivity of the heart to the cyclic changes in cardiac preload induced by mechanical ventilation "its normal range is $\leq 10\%$ ". Stroke volume variation = difference between maximal and minimal stroke volume divided by their mean during one respiratory cycle.
- **Pulse pressure variation** (see later).

Values $\geq 10\%$ change predict fluid responsiveness.

d- Parameters assessing the afterload: i.e., the resistance the heart has to overcome to eject blood.

- **Systemic vascular resistance (SVR).**
- **Systemic vascular resistance index (SVRI);** it is the SVR indexed to body surface area. Its normal range is 1600-2400 dyn.sec.cm⁻⁵.m².

e- Parameters assessing the contractility:

- **Index of left ventricular contractility (dPmx);** it indicates the maximum pressure increase in the aorta. $dP_{mx} = \Delta P_{max} / \Delta t$. It assesses the left heart contractility.
- **Global ejection fraction (GEF);** is the global stroke volume divided by global end-diastolic volume ($GEF = 4 \times SV / GEDV$). It assesses the global cardiac contractility. Its normal value is 25-35%.
- **Cardiac function index (CFI);** is the fraction of the preload volume pumped in one minute. It the cardiac output divided by global end-diastolic volume ($CFI = CO / GEDV$). It assesses the global cardiac contractility. Its normal range is 4.5-6.5 L/min.
- **Cardiac power output (CPO);** It is a surrogate parameter of the global cardiac performance. It is a nonspecific indicator of cardiac malfunctioning. It is the best predictor of mortality in patients with cardiogenic shock. $CPO = \text{Mean arterial blood pressure} \times CO$.
- **Cardiac power index (CPI);** It is CPO indexed to body surface area. Its normal range = 0.5-0.7 Watt/m².

f- Parameters assessing lung function:

- **Extravascular lung water (EVLW);** it is the amount of water content in the lungs indicating the amount of pulmonary edema at the bedside. It includes intracellular, interstitial, and intra-alveolar water (not pleural effusion).
- **Extravascular lung water index (ELWI);** it is the EVLW indexed to predicted body weight. Its normal range is 3-7 mL/kg.
- **Pulmonary vascular permeability index (PVPI);** it can differentiate between permeability or cardiogenic pulmonary edema. It assesses the relation between extra- and intra-vascular fluid. $PVPI = EVLW / \text{Pulmonary blood volume}$. Values between 1-3 are normal values of permeability and indicate cardiogenic (hydrostatic) lung edema, while values > 3 indicate permeability lung edema.

g- Parameter assessing oxygenation:

- **Central venous oxygen saturation (ScvO₂)** (via a standard central venous catheter): It allows early indication of an imbalance between oxygen consumption and oxygen delivery. There is a good clinical

correlation between $ScvO_2$ and $S\bar{u}O_2$. It is less invasive than $S\bar{u}O_2$ measurement. Its normal range is between 70-80%.

- **Oxygen delivery ($\dot{D}O_2$)** = $CO \times \text{hemoglobin} \times 1.38 \times SaO_2$.
- **Oxygen delivery index ($\dot{D}O_{2I}$)**; it is $\dot{D}O_2$ indexed to body surface area. Its normal range is 400-650 mL/min/m².
- **Oxygen consumption ($\dot{V}O_2$)** = $CO \times \text{hemoglobin} \times 1.38 \times (SaO_2 - ScvO_2)$.
- **Oxygen consumption index ($\dot{V}O_{2I}$)**; it is $\dot{V}O_2$ indexed to body surface area. Its normal range is between 125-175 mL/min/m².

Disadvantages of PiCCO:

- It needs both a central line and an arterial line that are in the femoral or axillary artery.
- Rapidly changing hemodynamic conditions will warrant repeated cold water injectate to reliably obtain a properly calibrated pulse contour analysis.
- The manufacturer recommends recalibration at least every 8 hours by another device which measures cardiac output.

b- Lithium Dilution Cardiac Output (LiDCO):

Physical Principles:

- It uses a peripheral injection of lithium ion 0.15-0.3 mmol with a 15-mL saline flush and a proprietary **arterial line containing a lithium sensor** to construct a dilution curve for the lithium ion.

$$\text{Cardiac output (L/min)} = \frac{\text{Lithium dose in mmol} \times 60}{(1 - \text{PCV}) \times Sd[Li]/dt}$$

Where: $Sd[Li]/dt$ = the area under the primary curve.

PCV = the packed cell volume $[Hb (g/dL)/34]$

A correction for PCV is necessary because lithium is distributed in the plasma.

- LiDCO assumes that arterial compliance changes with blood pressure and this change is similar in all humans.

Disadvantages of LiDCO:

- The original LiDCO device (the "pulse" model), like PiCCO, needs cardiac output to be measured by another device to calibrate its internal algorithm, but the more recent LiDCO device (the "rapid" model) does not need calibration.
- Lithium injections are affected by many factors such as lithium carbonate, hyponatremia, and some other drugs that contain quaternary ammonium ions (including muscle relaxants).

c- FloTrac/Vigileo:

Physical Principles:

By very difficult and sophisticated mathematics, FloTrac/Vigileo system uses the arterial pressure waveform which is analyzed in conjunction with demographic data consisting of age, height, weight, and sex. It can use the standard arterial line (figure 7-53).



Figure 7-53: FloTrac/Vigileo system

Advantages:

It does not need external calibration.

5- Arterial Pulse Pressure Variation:

Pulsus paradoxus is defined as an excessive decrease in systolic pressure seen with spontaneous ventilation in the presence of cardiac tamponade and other conditions. This phenomenon is used as a monitor according to the following facts:

- Arterial pulse pressure (systolic-diastolic pressure) is directly proportional to stroke volume and inversely related to arterial compliance (i.e., directly proportional to decreased distendibility).
- A positive pressure breath compresses the pulmonary venous system, causing an increase in left ventricular preload and an increase in stroke volume and arterial pulse pressure for a few beats.
- A positive pressure breath also decreases the venous return to the right heart by increasing intrathoracic pressure. This decreases the left ventricular filling; thus after a few beats of the increased pulse pressure that immediately follow a positive pressure breath, a decrease in the pulse pressure will follow.

In the presence of hypovolemia, the change in pulse pressure is greater than in normovolemia because in hypovolemia, the driving force for venous return, the mean circulatory filling pressure is reduced. The right atrium and vena cavae are thus more easily compressed, and the left ventricle is already operating on the steep portion of the Frank-Starling curve (figure 7-54).

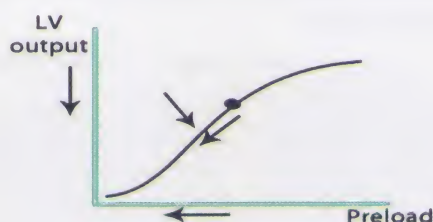


Figure 7-54: The Frank-Starling curve; left ventricular output (LV output) and preload

The parameters that are used for monitoring include (figure 7-55):

- **SPmax** = maximum systolic pressure.
- **SPref** = systolic pressure at end apnea (i.e., at the end of 5-second respiratory pause).
- **SPmin** = minimum systolic pressure.
- **Δ up** = difference between SPmax - SPref.
- **Δ down** = difference between SPref - SPmin.
- Δ down of ≥ 5 mm Hg predicts fluid responsiveness
- **Systolic pressure variations (SPV)** = maximum systolic pressure - minimum systolic pressure.
- **Pulse pressure variation (PPV)** is the change in pulse pressure over the respiratory cycle. It is also called **delta pulse pressure (ΔPP %)** = difference between maximum pulse pressure - minimum pulse pressure during one respiratory cycle divided by their mean

$$= \frac{100 \times (PP_{\max} - PP_{\min})}{[(PP_{\max} + PP_{\min})/2]}$$

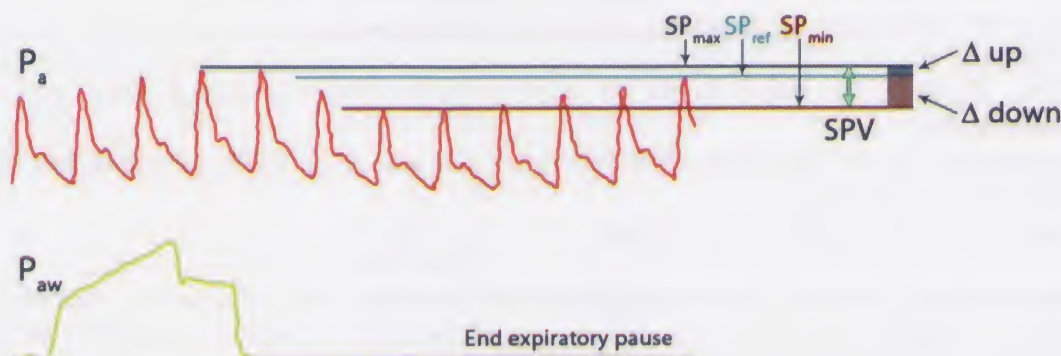


Figure 7-55: Pulse pressure variation

N.B.: **Pulse pressure variation (delta pulse pressure) and stroke volume variation** (their normal values are < 10%) are only applicable in patients on controlled mechanical ventilation with sinus rhythm.

Increased pulse pressure variation ($\Delta PP\%$) or stroke volume variation does not necessarily mean; there is a low cardiac output or hypovolemia, but its presence (i.e., > 10- 13%) is probably the **best predictor of fluid responsiveness** i.e., the blood pressure will increase with the administration of intravenous fluids or blood.

B- Non-Invasive Techniques

Advantages:

They provide beat-to-beat measurements and thus, are useful in following rapid changes in cardiac output.

Disadvantages:

They are less accurate than the Fick or indicator dilution techniques.

1- Doppler Ultrasonography:

Idea:

When ultrasound waves (with a frequency 1-10 MHz, either continuous or pulsed) are directed to a blood vessel, the sound waves will be reflected back with a frequency shift which is proportional to the velocity of blood flow. This is called the Doppler effect.

$$V = \frac{D f C}{2 f t \cos \theta}$$

Where V = the velocity of the blood.

Δf = the Doppler frequency shift.

f_t = the known frequency of the transmitted ultrasound wave.

C = the speed of sound in tissue.

θ = the angle between the direction of blood flow and the ultrasound beam

Stroke volume = average velocity during each heartbeat x the cross sectional area of the aorta

Cardiac output = stroke volume x heart rate

Methods of Application of the Ultrasound Beam:

- 1- **Trans-thoracic (suprasternal) Doppler:** The probe is applied via the suprasternal notch.
- 2- **Trans-tracheal Doppler:** The probe is attached to the distal end of an endotracheal tube.
- 3- **Trans-esophageal echocardiography** e.g., CardioQ: The probe is applied through the esophagus. The probe is inserted after the patient has been anesthetized and is positioned to yield the maximal signal.

Disadvantages:

They are **less accurate** than the Fick or indicator dilution techniques because:

- 1- The aortic diameter must be measured accurately, since the cross-sectional area = πr^2 . The aortic diameter can be measured either by:
 - pulsed A-mode echocardiography
 - or • nomogram.

Both are inaccurate because - the aorta is not completely circular.

- the aorta expands by up to 12% during systole.

- the site of the diameter measurement may not correspond to the position where the velocity is measured.

Therefore, this technique is inaccurate in patients with aortic diseases.

- 2- The shape of the velocity is as the laminar flow, where it is maximal at the center and minimal at the periphery; therefore, the beam should be aligned exactly along the central aortic axis; otherwise, inaccuracy occurs.

- 3- The direction of the ultrasound beam relative to the axis i.e., θ angle should be less than 20-30°; otherwise, large errors occur.

2- Thoracic Electrical Bio-impedance:

Idea:

Changes in thoracic volume lead to changes in thoracic resistance (bio-impedance). Two circumferential electrodes are placed around the neck and two around the upper abdomen. A small (< 1 mA), constant, high frequency (> 1 kHz) alternating current is passed between the electrodes around the neck and the resulting potential difference is detected by the abdominal electrodes. Measurements must be made with the subject holding his breath. The signal obtained represents changes in the thoracic blood volume and clearly resembles the pulse waveform.

Disadvantages:

It is unreliable because it is affected by:

- Electrical interference or pacemaker devices.
- Body movements and shivering.
- Dysrhythmias as atrial fibrillation, and marked tachycardia.
- Valvular regurgitation or intracardiac shunts.
- Mechanical ventilation, respiration, and PEEP.

Nowadays, new instruments enable measurements to be made during spontaneous or mechanical ventilation and give results which are closer to the indicator dilution results

3- Differential Fick's Principle or Non-Invasive Cardiac Output (NICO®) System:

It is a device that measures the cardiac output by using CO₂ **without using a pulmonary artery catheter**.

It is used in mechanically ventilated patients where carbon dioxide (CO₂) measurement is done during normal breathing interrupted with brief periods of rebreathing.

Usage:

- The device (containing sensors and a valve) is inserted between the endotracheal tube and the breathing circuit (the ventilator Y-connector). Every 30 min, the patient's inspired and expired gases are automatically diverted through the rebreathing loop for 50 seconds by a rebreathing valve (figure 7-56).

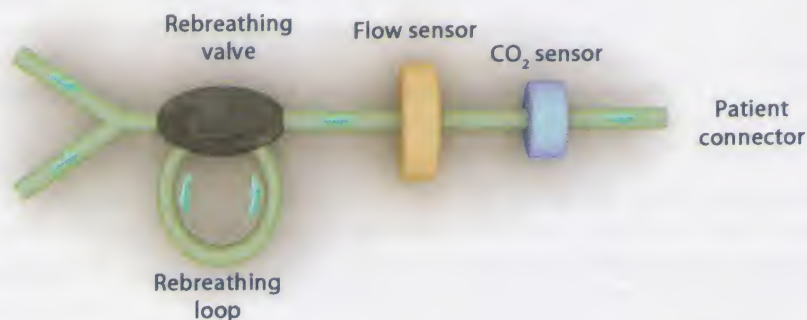


Figure 7-56: Differential Fick principle (NICO®) technique

It depends on the following principles:

As mentioned before, according to the Fick's principles,

$$\dot{Q}_t = \frac{\dot{V}_{CO_2}}{C\bar{v}CO_2 - CaCO_2}$$

Where:

\dot{V}_{CO_2} = CO₂ clearance or washout from the lungs.

$CaCO_2$ = arterial CO₂ content which is obtained by using the end-tidal CO₂ in a steady state.

$C\bar{v}CO_2$ = mixed venous CO₂ content which is obtained from a pulmonary artery catheter.

Addition of dead space and rebreathing allow mathematical calculation of cardiac output as follows:

Cardiac output during normal breathing = cardiac output during rebreathing = \dot{Q}_t

$$\dot{Q}_t = \frac{\dot{V}_{CO_2N}}{C\bar{v}CO_2N - CaCO_2N} \quad \text{and also} \quad \dot{Q}_t = \frac{\dot{V}_{CO_2R}}{C\bar{v}CO_2R - CaCO_2R}$$

$$\text{Therefore, } \dot{Q}_t = \frac{\dot{V}_{CO_2N}}{C\bar{v}CO_2N - CaCO_2N} = \frac{\dot{V}_{CO_2R}}{C\bar{v}CO_2R - CaCO_2R}$$

Where: N = normal

R = rebreathing

Knowledge of algebra allows the following assumption: If $\frac{a}{b} = \frac{c}{d}$ then $\frac{(a-c)}{(b-d)} = \frac{a}{b} = \frac{c}{d}$

and if applied to the above equation then:

$$\dot{Q}_t = \frac{\dot{V}_{CO_2N} - \dot{V}_{CO_2R}}{(C\bar{v}_{i-2} N - C_{aCO_2N}) - (C\bar{v}_{CO_2R} - C_{aCO_2R})}$$

During rebreathing, venous CO₂ should be the same as under normal conditions and CV_{CO₂N} = CV_{CO₂R} and thus this equation becomes:

$$\dot{Q}_t = \frac{\dot{V}_{CO_2N} - \dot{V}_{CO_2R}}{C_{aCO_2R} - C_{aCO_2N}}$$

All these variables can be measured by the device.

- When the Fick's principle is applied as above, the resulting value for cardiac output represents only the fraction of the flow that participates in gas exchange i.e., the pulmonary capillary blood flow. Therefore, the shunt flow should be estimated and added to the value obtained from measurement to extract the cardiac output measurement. This is done by taking a value for the inspired oxygen concentration supplied to the equipment by the operator, and comparing the expected oxygen saturation with oxygen saturation measured by means of pulse oximetry.

Disadvantages of NICO® system:

- To use this device, the patient must be on positive pressure ventilation with stable tidal volume and respiratory rate.
- Difficulty in using this mathematical equation.
- The difference in N and R CO₂ is usually quite small (i.e., < 10 mm Hg); therefore, this small difference in measurement may lead to large changes in calculated cardiac output.
- Shunted blood containing CO₂ is eliminated from consideration in this model or calculated as above.

4- Magnetic Resonance Imaging (MRI):

- Velocity encoded phase contrast magnetic resonance imaging is the most accurate technique for measuring flow in large vessels. MRI flow measurements has been shown to be highly accurate compared to measurements with both Fick principle and thermodilution.
- Velocity encoded MRI based on detection of changes in the phase of proton procession. These changes are proportional to velocity of movement of those protons through a magnetic field with a known gradient.
- The result of MRI scan is two sets of images for each time point in cardiac cycle. One is an anatomical image and the other is an image where the signal intensity in each pixel is directly proportional to through-plane velocity. Average velocity in a vessel i.e., aorta or pulmonary artery, is hence quantified by measuring average signal intensity of the pixels in cross section of vessel, and then multiplying by a known constant.
- The flow is calculated by multiplying the mean velocity by cross-sectional area of vessel. This flow data can be used to graph flow versus time. The area under flow versus time curve for one cardiac cycle is stroke volume.
- The length of cardiac cycle is known and determines heart rate, and thereby cardiac output can be as product of stroke volume and heart rate.
- MRI is typically used to quantify the flow over one cardiac cycle as the average of several heart beats, but it is also possible quantify the stroke volume in real time on a beat-for-beat basis.
- While MRI is an important research tool for accurately measuring cardiac output, it is currently not clinically used for hemodynamic monitoring in the emergency or intensive care setting. Cardiac output measurement by MRI is currently routinely used as a part of clinical cardiac MRI examinations.

5- The Bradley Method:

It depends on **Ohm's law** where the voltage gradient across a circuit equals the product of the current and the resistance ($V = C \times R$).

In the systemic circulation, the pressure gradient across the circuit (mean arterial pressure - central venous pressure) measured in mmHg = cardiac output (L/min) × peripheral vascular resistance (in wood units).

Assessment is done as follows:

1. Assessment of the pressure gradient:

Central venous pressure estimated clinically or by a central venous catheter.

Mean arterial pressure estimated by invasive or non-invasive methods.

2. Assessment of the peripheral vascular resistance (PVR):

It is quantified in wood units. This assessment assumes that a progressive increase in PVR is associated with a progressively proximal level of vasoconstriction. So;

- If the PVR is very high (> 40 wood units), there will be a palpable cut off between warm and cold skin above the elbow.
- With progressive dilatation, this cut off level will move distally, until the whole arm and fingers are warm (20 wood units).
- With more advanced dilatation, the fingers when lightly squeezed together, as in a hand-shake will have a palpable pulsatile feel (15 wood units).
- When markedly vasodilated (< 10 wood units), the forearms can be felt to pulsate when lightly gripped circumferentially by both hands.

3. By using the data above, cardiac output (L/min) and stroke volume (mL) can be calculated.

VIII- Trans-esophageal Echocardiography (TEE)

It is invented by Yasu Oka in 1976.

Principles:

M-mode, 2-D scanning and other types have been discussed before in the chapter of "Basic physics for anesthesia and intensive care".

By studying **velocity-time waveform** (Fourier transform spectral analysis) many derived variables can be obtained as (figure 7-57):

- **Cycle time** correlates with systole and diastole times.
- **Flow time** correlates with the time of systolic flow in the aorta.

$$\text{Corrected flow time} = \frac{\text{Flow time}}{\text{Square root of cycle time}}$$

The flow time indicates left ventricular filling and volume status and is inversely proportionate to systemic vascular resistance.

- **Peak velocity** correlates with left ventricular contractility and function.
- **Stroke volume** can be obtained from the **area under the waveform** and the **stroke distance**.

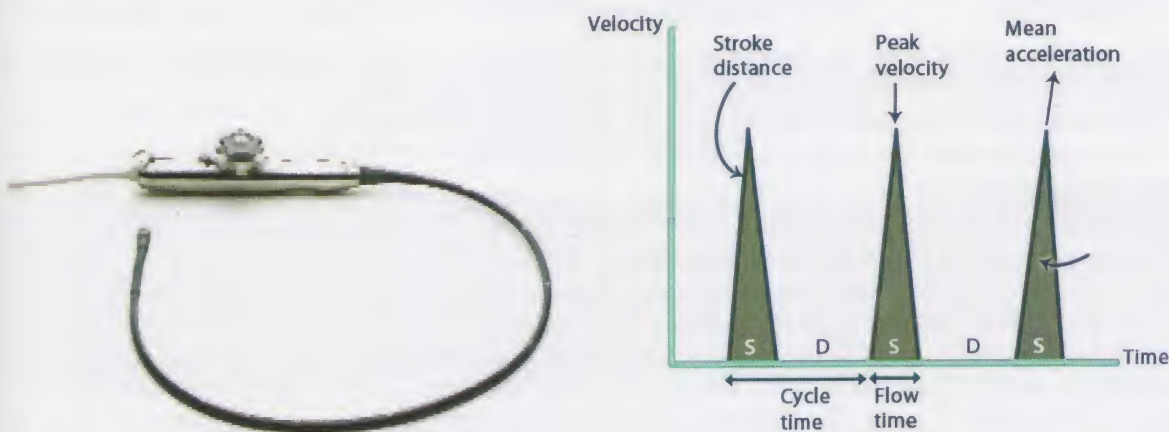


Figure 7-57: TEE (left) and velocity-time waveform (right)

TEE is an ultrasound transducer which is mounted on the end of a flexible endoscope. It is inserted into the esophagus at 35–40 cm. **The patient should be anesthetized;** therefore, it is unsuitable during induction and intubation. Before its introduction, a gastric tube is introduced to take out excessive stomach content and air.

Technique and Basic TEE Views:

There are 4 main views of TEE. Each view can show certain structures.

Views (Acoustic Window) and Depth from the Incisors	Cross-section	Multi-plane angle range	Structures Imaged
1- Upper esophageal (UE) (20-25 cm)	- Aortic arch long axis (s) - Aortic arch short axis (t)	0° 90°	- Aortic arch, left BC vein. - Aortic arch, PA, PV, left BC vein.
2- Mid esophageal (ME) (30-40 cm)	- Four-chamber (a) - Mitral commissural (g) - Two-chamber (b) - Long axis (c) - RV inflow-outflow (m) - AV short axis (h) - AV long axis (i) - Bicaval (l) - Asc aortic short axis (o) - Asc aortic long axis (p) - Desc aortic short axis (q) - Desc aortic long axis (r)	0-20° 60-70° 80-100° 120-160° 60-90° 30-60° 120-160° 80-110° 0-60° 100-150° 0° 90-110°	- LV, LA, RV, RA, MV, TV, IAS. - MV, LV, LA. - LV, LA, LAA, MV, CS. - LV, LA, AV, LVOT, MV, asc aorta. - RV, RA, TV, RVOT, PV, PA. - AV, IAS, Coronary ostia, LVOT, PV. - AV, LVOT, Prox.asc.aorta, Right PA. - RA, SVC, IVC, IAS, LA. - Asc. Aorta, SVC, PA, Right PA. - Asc. Aorta, Right PA. - Desc thoracic aorta, left pleural space. - Desc thoracic aorta, left pleural space.
3- Trans-gastric (TG) (40-45 cm)	- Basal short axis (f) - Mid short axis (d) - Two-chamber (e) - Long axis (j) - RV inflow (n)	0-20° 0-20° 80-100° 90-120° 100-120°	- LV, MV, RV, TV. - LV, RV, Pap m. - LV, MV, Chordae, Pap m, CS, LA. - LVOT, AV, MV. - RV, TV, RV, TV, Chordae, Pap m.
4- Deep trans-gastric (DTG) (45-50 cm)	- Long axis (k)	0-20° Ante-flexion	- LVOT, AV, asc.aorta, arch.

Abbreviations:

BC vein = Brachio-cephalic vein.	MV = Mitral valve.	Pap m = Papillary muscles.
PA = Pulmonary artery.	TV = Tricuspid valve.	Prox = Proximal.
PV = Pulmonary valve.	IAS = Inter-atrial septum.	AV = Aortic valve.
LV = Left ventricle.	LAA = Left atrial appendage.	SVC = Superior vena cava.
LA = Left atrium.	CS = Coronary sinus.	IVC = Inferior vena cava.
RV = Right ventricle.	RVOT = Right ventricular outflow tract	RPA = Right pulmonary artery.
RA = Right atrium.	LVOT = Left ventricular outflow tract.	asc. = ascending & desc = descending.

From the previous table, you can detect the views required for examination of different structures for examples, for mitral valve TEE examination, the following views are needed:

- Mid esophageal view; four-chamber, mitral commissural and long axis.
- Trans-gastric: basal short axis, two-chamber, and long axis.

Clinical Applications:

1. Assessment of Cardiovascular Pathology:

It has advantages over epicardial echocardiography:

- 1- It does not interfere with or delay the surgical procedure.
- 2- It does not increase the risk of arrhythmias and infection.
- 3- It can be performed continuously **pre-, intra-, and postoperatively**; therefore, it can assess the adequacy of the repair.

It assesses both **global ventricular function** (systolic or diastolic, left or right ventricular or both) and **regional ventricular function** i.e., Segmental Wall Motion Abnormality (SWMA).

It is especially indicated in conditions such as:

- **aortic injury or dissection**,
- **aortic atheroma and atherosclerosis** (especially in the thoracic aorta, the distal ascending aorta and part of the arch that are difficult to visualize because the trachea does not permit the transit of ultrasound waves),
- **air embolism** (TEE can detect small air bubbles down to 1 mm in diameter),
- **patent foramen ovale**,
- **valvular diseases**,
- cardiac tumors as **left atrial myxoma**,
- during CABG surgery, and
- **congenital heart disease**.

2. Assessment of Hemodynamics:

It can detect:

- Left ventricular preload and contractility.
- Left ventricular filling pressure (left atrial pressure).
- Cardiac output (as cardiac output = stroke volume x heart rate)
 - by • Measuring velocity of blood flow by Doppler and the cross-sectional area of flow by 2-D echo e.g., at the aortic root or at the aortic valve.
As stroke volume = average blood velocity over a minute x cross-sectional area.
 - or • Measuring the ventricular volume by 2-D or M-mode images at end-systole and at end-diastole.
Stroke volume = difference between these two values.

The relationship between hemodynamic parameters is shown in figure 7-58.

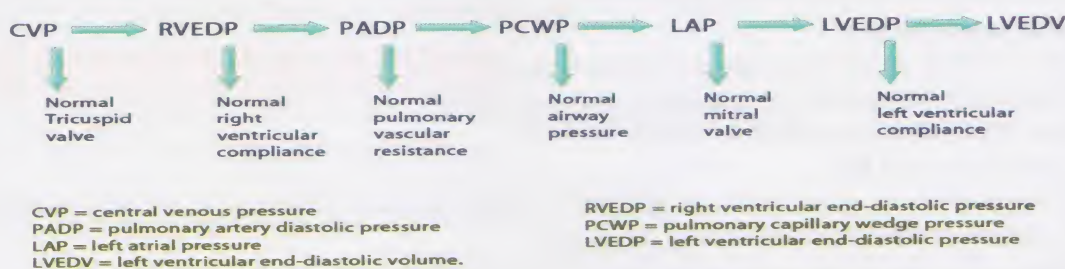


Figure 7-58: Relationship between hemodynamic parameters

- Acute hypotension:

It is used as a guide for administration of intravenous fluids, inotropes and vasopressors.

It allows early detection of decreased preload before it leads to significant hypotension.

It facilitates prompt differential diagnosis of acute hypotension as follows:

Cause	LVED area	Ejection Fraction
Hypovolemia	↓↓	↑↑ > 0.8 (well contracting heart)
Left ventricular failure	↑↑	↓↓ < 0.2 (poorly contracting heart)
Decreased systemic vascular resistance, aortic or mitral regurgitation, or ventricular septal defect.	Normal	↑↑ > 0.8 (well contracting heart)

Where ↓ = decrease

↑ = increase

3. Detection of Ischemia:

Ischemic segments of the heart do not contract normally. During acute ischemia, **segmental wall motion abnormalities (SWMA)** occur within seconds of the onset of ischemia. It precedes and may occur without ST segment changes i.e., **TEE has a greater advantage than ECG.**

The classes of SWMA are:

Class of Motion	Wall Thickening	Change in Radius
1- Normal	Marked	> 30 % decrease
2- Mild hypo-kinesis	Moderate	10 - 30 % decrease
3- Severe hypo-kinesis	Minimal	0 - 10 % decrease
4- Akinesis	None	None
5- Dyskinesis (paradoxical)	Thinning	Increase

N.B.: Change in the radius means a decrease in the length of an imaginary radius from the endocardium to the centre of the left ventricular cavity, in the mid-papillary cross-section during systole.

Not all SWMA are indicative of myocardial ischemia. They can occur in **myocardial infarctions, myocardial stunning and myocarditis**. However, sudden severe decrease or cessation of SWMA is almost always due to myocardial ischemia.

Role of TEE in Non-Cardiac Surgery:

- 1- High risk major general surgeries.
- 2- Vascular surgeries.
- 3- Eclamptic patients.
- 4- Neurosurgeries especially in sitting craniotomy.
- 5- Blunt chest trauma: to detect pericardial effusion, tamponade, myocardial contusion, aortic rupture, or dissection).
- 7- Orthopedic surgery to detect fat and air embolism.

- 8- Liver transplantation.
- 9- Postoperatively in post-anesthetic care units (PACU) or intensive care units (ICU).

In these surgeries, TEE is used to assess:

- Cardiovascular pathology as air embolism.....etc.
- Hemodynamics as cardiac output and causes of hypotension.....etc.
- Myocardial ischemia as SWMA.....etc.

Contraindications:

- 1- Aortic coarctation: as it gives no meaningful signals.
- 2- Use of intra-aortic balloon pump: as it gives no meaningful signals.
- 3- Thoracic aortic aneurysm: as it gives no meaningful signals.
- 4- Moderate to severe aortic regurgitation as it reverses flow throughout the whole diastole.
- 5- Local pathology: as esophageal or gastric varices, esophageal stricture, recent surgery, or cancer.
- 6- Marked coagulopathies.
- 7- Surgery in sitting position (a relative contraindication).
- 8- Previous mediastinal radiation (a relative contraindication).
- 9- Oropharyngeal trauma (a relative contraindication).

Complications of TEE:

- 1- **Stress response:** occurs in awake or minimally sedated patients (outpatients) on swallowing the TEE probe; therefore, it is better to anesthetize the patient.
- 2- **In infants:** The relative large size of the TEE probe may cause:
 - obstruction of the airway distal to the endotracheal tube,
 - compression of the descending aorta,
 - inadvertent extubation,
 and - endobronchial advancement of the endotracheal tube.
- 3- **Increased risk of trauma:** It may cause loose teeth, **pharyngeal or esophageal injury**.
- 4- **In congenital heart lesions:** There are increased possibilities of coagulopathies or congenital vertebral anomalies; therefore, care should be taken.

IX- Regional Blood Flow Measurement

Measurement of Cerebral Blood Flow

See later "Monitoring of nervous system".

Measurement of Renal Blood Flow

Renal Plasma Flow (RPF)

It is measured by the clearance method which is based on the **Fick's principle**. The clearance of **para-amino-hippuric acid (PAH)** is used because it is **completely cleared** in one passage via the kidneys as it is filtered by the glomeruli and secreted by the renal tubules:

$$\text{RPF} = \text{clearance of PAH} = \frac{U_{\text{PAH}} \times V}{R_{\text{PAH}} - R_{\text{VPAH}}}$$

$$\text{As } R_{\text{VPAH}} \text{ is negligible, so } = \frac{U_{\text{PAH}} \times V}{R_{\text{PAH}}} = \frac{U_{\text{PAH}} \times V}{P_{\text{PAH}}} = 660 \text{ mL/min}$$

Where: U_{PAH} = Urine concentration of PAH in mg/mL.

R_{PAH} = Renal artery concentration of PAH in mg/mL.

R_{VPAH} = Renal vein concentration of PAH in mg/mL.

P_{PAH} = Plasma concentration of PAH in mg/mL.

V = Urine volume in mL/min.

N.B.: Actually, as only 90% of PAH is excreted by the human kidney, the clearance of PAH underestimates RPF by approximately 10%. To improve the accuracy, RPF can be estimated from the disappearance curve of intravenously injected *o*-iodohippuric acid (hippuran) labeled with ^{131}I or ^{125}I , eliminating the potential error introduced by timed urine collection.

Renal Blood Flow (RBF) It is obtained from renal plasma flow as follows:

$$\text{RBF} = \frac{\text{RPF}}{1 - \text{hematocrit}} = 1200 \text{ mL/min.}$$

Measurement of Hepatic Blood Flow

a- Measurement of Total Hepatic Blood Flow:

It is measured by the indicator dilution technique where the indicator is labeled red cells or serum albumin. The indicator is injected into the hepatic artery or portal vein and the dilution curve is obtained by hepatic venous blood sampling.

b- Measurement of Hepatocyte Clearance:

By using clearance of bromosulphthalein (BSP) which is cleared by the hepatocytes and excreted into the bile.

c- Measurement of Reticulocyte Clearance:

It is done by using clearance of colloidal gold or sulphur.

d- Hepatic Drug Extraction:

It is done by using clearance of lignocaine or propranolol.

X- Measurement of Blood Loss

Losses > 15% in adults and > 10% in pediatrics should be replaced by blood.

This can be done by one of the following methods:

1- Visual Estimation of Swabs and Abdominal Packs:

Surgical swabs and sponges (4 x 4 cm): lightly soaked = 5 mL.
 moderately soaked = 10 mL
 fully soaked = 15 mL
 Surgical packs and pads (15 x 15 cm): fully soaked = 100-150 mL

It is a rough method.

2- Weighing of Swabs and Packs Before and After the Use:

One mL of blood weighs about 1 g; therefore, weighing the swabs and packs before (dry) and after the use (soaked) may give estimation of the amount of blood loss especially in pediatrics.

It is a rough method because the blood may be diluted with saline or the packs and swabs may be wetted before use. It also ignores blood lost on drapes, gowns...etc, and with water evaporation.

3- Measurement of Blood in the Suction Container:

The blood in the suction container is measured after subtracting washing fluids. It is a rough method because the blood may be diluted by saline.

4- Hemoglobin Extraction Dilution Method:

It is an accurate method.

The blood on swabs, packs, and sponges is mixed with 100 liters of water by bubbles of compressed air in a washing machine. The hemoglobin (Hb) of the patient's blood is measured and the hemoglobin of the blood stained water is estimated by a photocell and a light source i.e., by **colorimetry**. The blood loss can be estimated as follows:

Total Hb in 100 liter reservoir = concentration of Hb in the reservoir × reservoir volume

$$\text{Blood loss} = \frac{\text{Total Hb in the water reservoir (gm)}}{\text{Concentration of the Hb of the patient (gm/L)}}$$

For example, if the patient's Hb is 15 g% (i.e., 150 g/L) and the reservoir's Hb concentration is 0.2 g% (i.e., 2 g/L) then:

$$\text{Total Hb in the 100 liter reservoir} = 2 \text{ g/L} \times 100 \text{ L} = 200 \text{ g}$$

$$\text{So, blood loss} = \frac{200}{150} = 1.33 \text{ liter.}$$

5- Electrical Conductivity Method:

It is an accurate method. The blood on swabs, packs, and sponges is extracted in a volume of water. The amount of blood loss is **calculated from changes in the electrical conductivity of blood stained water** by Wheatstone bridge circuit. The instrument is bulky and expensive.

6- Weighing the Patient Before and After:

Especially in case of exchange blood transfusion as in extracorporeal circulation.

PART 2: MONITORING OF THE RESPIRATORY SYSTEM

Monitoring of the respiratory system includes:

- 1- Clinical monitoring.
- 2- Monitoring and alarms during mechanical ventilation.
- 3- Precordial and esophageal stethoscope.
- 4- Spirometry.
- 5- O₂ monitoring.
- 6- CO₂ monitoring.
- 7- Anesthetic gas analysis.
- 8- Pulmonary function tests.

I - Clinical Monitoring

It is **the most important** and includes:

- 1- Patient's color: Although it is important clinically, it has too many limitations as follows:
 - Different observers may give different assessment of cyanosis.
 - Ambient lighting can bias judgment.
 - An anemic patient may have critically low oxygen saturation and yet does not have sufficient deoxyhemoglobin in the arterial blood to reveal cyanosis.
 - In patients with a reduced cardiac output or in capillaries where stasis is present, cyanosis may be unrelated to arterial saturation.

Cyanosis occurs when deoxyhemoglobin reaches ≥ 5 g% in the capillaries.

- 2- Respiratory rate.
- 3- Adequacy of chest movement.
- 4- Movement of the reservoir bag or ventilator bellows.
- 5- Frequent auscultation of both lung fields by **binaural stethoscope** to detect:
 - quality of air entry, (obstruction, pneumothorax),
 - intubation of bronchus,
 - presence of secretions,
 - and - wheezes (bronchospasm),

In addition to - heart rate regularity,
and - heart tones as muffled tones are associated with decreased cardiac output (especially in pediatrics).

- 6- Some ventilators make a regular noise during part of the ventilatory cycle which is a valuable audible monitor.

N.B.: Signs of respiratory obstruction:

- Nasal flaring.
- Tracheal tug.
- Paradoxical abdominal movement.
- No bag inflation.
- Stridor: Inspiratory stridor indicates extra-thoracic cause, and expiratory stridor indicates intra-thoracic cause.

II- Monitoring and Alarms during Mechanical Ventilation

They are discussed in the chapter of "Intensive (Critical) Care".

III- Precordial and Esophageal Stethoscope

Indications:

It can be used in all anesthetized patients because it is cheap, non-invasive, and free from electrical interference.

Contraindications:

Esophageal varices or strictures.

Value:

The same as binaural stethoscope.....see before.

In addition to detection of **air embolism** by hearing the **classical Mill wheel murmur** as the air is audible when it enters great veins or heart chambers.

Technique:

A- Precordial Stethoscope (Wenger Chest Piece):

It is a heavy, bell-shaped piece of metal placed over the chest or suprasternal notch (figure 7-59). It has different sizes.

It is fixed by double-sided adhesive disks which provide an acoustic seal to the patient's skin. A molded monaural earpiece allows simultaneous monitoring of the stethoscope and operating room environment.

B- Esophageal Stethoscope:

It is a soft plastic catheter (8-24 F) with a balloon-covered distal opening with an ear-piece, or can be connected to a microphone (figure 7-60). Its use is limited to intubated patients.

In some designs, there are:

- temperature probes,
- ECG leads,
- and • atrial pacemaker.

IV- Spirometry

Indications:

- 1- Mechanical ventilation.
- 2- Affected respiratory mechanics such as - one lung anesthesia,
and - severely asthmatic patients.

There are many types of respirometers; the most common is the Wright respirometer.

For more details, see before in "Flow and volume measurement".



Figure 7-59: Precordial stethoscope

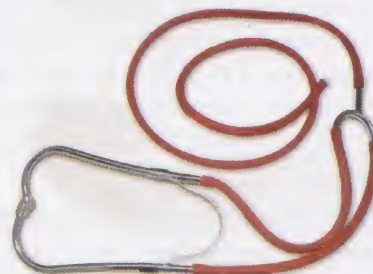


Figure 7-60: Esophageal stethoscope can be connected either to a microphone (left) or bi-auricular ear-pieces (right)

V- O₂ Monitoring

A- O₂ Monitoring Outside the Body (O₂ Delivery to the Patient):

It includes:

- 1- O₂ failure alarms.
- 2- O₂ analyzers (detection of inspired O₂ concentration in gas mixtures).
 - Fuel cell (Galvanic O₂ analyzer).
 - Clark electrode (Polarographic) (O₂ electrode).
 - Paramagnetic analyzer.

B- O₂ Monitoring inside the Body (O₂ Delivery to the Tissues, Monitoring of Tissue Oxygenation):

Physiology:

O₂ Delivery (DO₂):

$$\begin{aligned} \text{DO}_2 &= \text{cardiac output} \times \text{CaO}_2 \quad \text{mL/min} \\ &= \text{cardiac output} \times ([\text{Hb g/dL} \times 1.38 \times \text{SaO}_2 \text{ \%}] + [0.003 \times \text{PaO}_2 \text{ mmHg}]) \end{aligned}$$

Oxy-Hb Dissociation curve is discussed in details in chapter "Anesthesia & Respiratory Diseases".

Oxygen Monitoring includes:

I- Global Tissue Oxygenation:

1- Clinical Monitoring:

Tissue perfusion is discussed above.

2- O₂ Delivery (Transport) Monitoring:

- 1- **Cardiac output (CO)** by
 - CO measurement
 - Arterial blood pressure
 - Central venous pressure
 - Pulmonary artery pressure
 - Pulmonary capillary wedge pressure.
- 2- **Hemoglobin (Hb)** level.
- 3- **Arterial O₂ saturation (SaO₂)** by pulse oximetry.
- 4- **Arterial O₂ tension (PaO₂)** in vivo by
 - Miniature Clark electrode.
 - Fiberoptic O₂ sensor.
 - Transcutaneous O₂ tension.
 - Conjunctival O₂ tension.
 - Mass spectrometer inserted in an intravenous catheter.

3- O₂ Uptake Monitoring:

- 1- $\dot{V}\text{O}_2$ by pulmonary artery oximetry.
- 2- Serum lactic acid measurement.

II- Regional Tissue Oxygenation:

- 1- Subcutaneous and intravenous oximetry.
- 2- Cerebral oximetry.
- 3- Gastric intra-luminal tonometry.

Oxygen Analyzers

Value:

An oxygen analyzer should be placed **in the inspiratory limb** of the anesthetic delivery system (not into the fresh gas flow) to measure the inspired oxygen concentration and ensure that the anesthesia machine is delivering an adequate oxygen concentration to the patient especially with low flow or closed circuits. Sometimes it is placed **in the expiratory limb** of the anesthetic breathing system to compare the expired O₂ with the value of the inspired oxygen to calculate the patient's oxygen consumption. **An alarm device** should be present and set to give a signal when oxygen concentration is below 30%.

Types:

A) Electrochemical Sensors:

These devices convert chemical energy into electrical energy. There are two types:

1- O₂ Electrode (Clark or Polarographic Electrode)

It is invented by Clark in 1956.

Uses:

It measures O₂ tension (partial pressure of O₂):

- **In a blood sample.** It is the electrode present in the blood gas analyzer (together with CO₂ and pH electrodes).
- **In a gas mixture** (but it is not commercially available).

Idea:

The electrode consists of:

- **An anode: silver/silver chloride.**
- **An electrolyte solution: KCl.**

Chloride ions of KCl combine (react) with silver at the anode causing production of electrons.

- **A cathode: platinum wire.**
- **A plastic membrane** which is usually **Teflon**, polyethylene or polypropylene, each being permeable to oxygen.

O₂ will diffuse from the sample via the plastic membrane and reach the cathode. Because O₂ will combine with electrons and water, hydroxyl ions will be produced.



So, the current flow depends on the uptake of O₂ at the cathode; therefore, it depends on O₂ concentration and partial pressure i.e., the more O₂ is available the more electrons are taken up at the cathode and thus, the more current flows (figure 7-61).

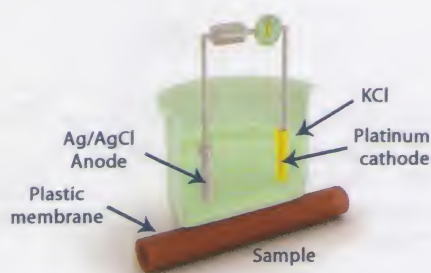


Figure 7-61: Clark electrode

A battery with a voltage of 0.6v is applied between the electrodes.

A **miniature O₂ Clark electrode** mounted on the tip of a catheter is used for **continuous O₂ tension measurement of blood** in the blood vessels and the heart, but it is subjected to a build-up of fibrin which alters the electrode sensitivity.

A **portable O₂ Clark electrode** is available where the **electrolyte solution is in the form of a gel** but it has a short life span.

Disadvantages:

- 1- In the presence of **halothane**, a **false high reading** occurs as it is reduced by polarizing voltage (0.6 v). To avoid this problem, use an electrode membrane which is not readily permeable to halothane.
- 2- **Plastic membranes** should be checked and replaced if punctured or covered by protein deposits.
- 3- **The arterial sample** must be taken anaerobically and heparinized to prevent clotting.
- 4- **Analysis should be done as soon as the samples are taken** as O₂ tension falls steadily especially at room temperature due to red blood cells metabolism. If the delay is unavoidable, a correction factor is applied for time delay or samples are kept in a container full of ice (both are less accurate).
- 5- The device should be maintained at a **constant temperature (37°C)** during use.

2- Fuel Cell (Galvanic O₂ Analyzer)

Uses:

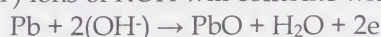
It measures O₂ tension (partial pressure of O₂) in a **gas mixture**.

Idea: is similar to the O₂ electrode.

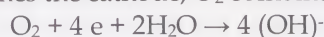
The cell is formed of:

- **An anode:** formed of **lead**.
- **An electrolyte solution:** **KOH**.

(OH⁻) ions of KOH will combine with the lead at the anode causing production of electrons.



- **A cathode:** formed of a **silver or gold mesh**. O₂ diffuses from the sample through the plastic membrane and reaches the cathode, O₂ combines with electrons and water producing hydroxyl ions.



Therefore, the current flow depends on the uptake of O₂ at the cathode and thus, it depends on O₂ concentration and partial pressure (figure 7-62).

No battery is needed in the fuel cell because the cell itself produces a voltage, thus acting as a battery.

This device is placed in the inspiratory limb of the breathing system.

Advantages:

- 1- It has a response time of 20-30 sec.
- 2- It is accurate within $\pm 3\%$.
- 3- It is calibrated simply by using air.
- 4- It is not affected by humidity.
- 5- It is inexpensive.

Disadvantages:

- 1- If the device is placed between the gas outlet port of an anesthetic machine and a gas-driven ventilator e.g., Manley type, the total gas pressure to which the detector is subjected increases by 25- 30 % by back pressure. This increases the partial pressure of O₂ by the same percentage. Therefore, false high O₂ concentration is recorded. To overcome this problem, the device is placed in the inspiratory limb of the breathing system i.e., after the ventilator.

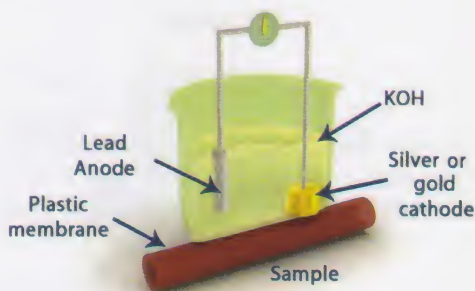


Figure 7-62: Fuel cell

2- In presence of N_2O , it diffuses into the fuel cell and reacts at the anode with lead and KOH, causing production of nitrogen which alters the pressure inside the device and **may damage it**. To overcome this problem, especially designed cells for anesthetic machines are available, but have a shorter life span than the standard ones.

3- Like other batteries, it eventually **expires within several months**.

4- Its results are affected by the temperature, but **temperature compensation** may be achieved by means of a thermistor placed within the fuel cell.

B) Paramagnetic Analyzer or Sensor:

Uses:

It measures O_2 tension (partial pressure of O_2) in a gas mixture.

Idea:

- O_2 is paramagnetic i.e., attracted into a magnetic field (because the electrons in the outer shell of O_2 molecule are unpaired), but most other gases e.g., nitrogen are weakly diamagnetic i.e., repelled from a magnetic field.

A gas-tight chamber or cell containing two glass spheres connected in a dumb-bell arrangement are placed in a non-uniform magnetic field.

- The dumb-bell is suspended on a filament so that it can rotate and the glass sphere becomes filled with nitrogen. The orientation of the dumb-bell in the magnetic field is determined by the tension of the suspending filament (figure 7-63).

- If O_2 is added to the cell, it is attracted to the magnetic field and displaces the glass sphere containing N_2 resulting in dumb-bell rotation until the force of this displacement is balanced by the tension of the filament which is measured by attaching a mirror to the dumb-bell suspension. Thus, the position of a light beam reflected from this mirror provides an indication on a scale.

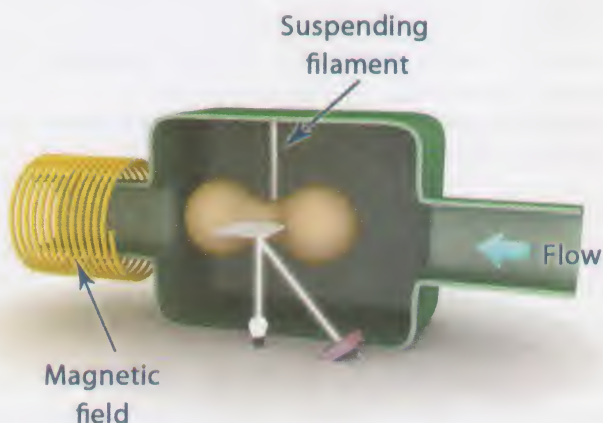


Figure 7-63: Paramagnetic analyzer

• In some devices called **null-deflection analyzers**, the reflected light beam falls on a photocell producing a current that flows via a coil around the dumb-bell. Therefore, an opposing magnetic field is produced which keeps the dumb-bell in its resting position. So, the amount of the current gives a measure of the O_2 concentration in the analyzer. These null-deflection analyzers give very accurate results about 0.1%.

• In other devices called **pulsed-field paramagnetic oxygen analyzers** (figure 7-64), there are two streams of gas (a **sample gas** and a **reference gas** which is usually air). Both streams of gas flow through **upstream constrictions** then to a chamber where they are separated by a **differential pressure transducer**. Both gases are exposed to a **pulsed magnetic field** that is generated by an electromagnet, which is switched on and off alternatively.

When the magnetic field is switched on, oxygen molecules are attracted and move toward the field producing a reduction of pressure in the volume of the sample gas. This reduction in pressure causes a deflection of the pressure transducer diaphragm towards the sample gas side.

When the magnetic field is switched off, the differential pressure is no longer present and the transducer diaphragm returns to its central position.

Therefore, the magnitude of the alternating pressure at the transducer is used as a measure of the oxygen partial pressure in the sample gas.

Advantages:

- 1- It is self-calibrating.
- 2- It has no consumable parts.
- 3- It has a fast response time.

Disadvantages:

- 1- It needs calibration before use with 100% N_2O and 100% O_2 .
- 2- Like many other gas analyzers, it is affected by water vapor. When the water vapor is added to a previously dry mixture of gases, the concentration of the other components will be reduced due to the partial pressure of the water vapor. Therefore:

- Gas samples should be dried 1st by passage via silica gel.
- or • If humidified gases are analyzed at $37^\circ C$, O_2 concentration in the dry mixture can be calculated as:

$$O_2 \text{ concentration} = \frac{\text{Partial pressure (humidified at } 37^\circ C)}{\text{Barometric pressure} - \text{saturated vapor pressure of water at } 37^\circ C}$$

This is because the partial pressure of water vapor will decrease the partial pressure of other components in the sample.

- 3- As with fuel cell, its output is affected by the temperature.

N.B.: The inspired O_2 concentration can also be measured by a multi-gas analyzer such as:

- Mass spectrometry.
- Raman gas analyzer.
- Respirometer gas monitor.

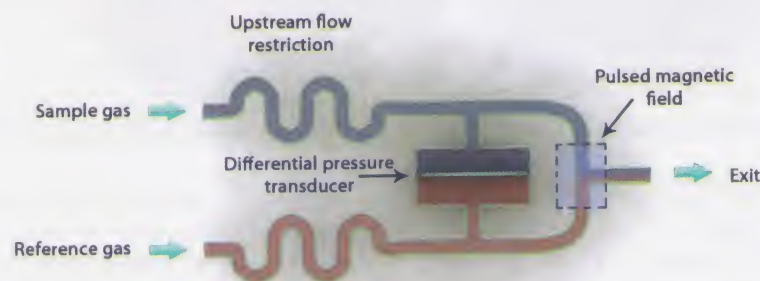


Figure 7-64: Pulsed-field paramagnetic analyzer

Pulse Oximetry

Value:

It is one of the most essential monitors for routine use in anesthesia and intensive care.

- 1- It measures **O_2 saturation** of Hb in arterial blood.
- 2- It measures **heart rate**.
- 3- It gives an idea about **tissue perfusion** by pulse waveform.

- Increased pulse amplitude indicates vasodilatation.
- Decreased pulse amplitude indicates vasoconstriction or hypovolemia.
- Area under the curve indicates stroke volume.
- The dicrotic notch moves down with vasodilatation.

Therefore, the pulse oximeter can be used for assessment of blood flow e.g., in a revascularized limb, a reanastomosed limb or in a digit after or during surgery.

$$\text{N.B.: O}_2 \text{ saturation} = \frac{\text{Oxygen content of Hb mL/dL}}{\text{Oxygen capacity of Hb mL/dL}} \times 100$$

O₂ capacity is the maximum oxygen content of hemoglobin i.e., when the Hb is 100% saturated.

- N.B.: - Transmission spectrophotometry is used in pulse oximetry.
 - Reflection spectrophotometry is used in cerebral, pulmonary, and intravascular oximetry.
 - Absorption spectrophotometry is used in capnography.

Principles:

Based on **transmission spectrophotometry and plethysmography**

A- Oximetry Principle (Spectrophotometry):

When specific wavelength radiations pass through a solution sample, the compound of interest absorbs these specific radiations and the quantity of absorption depends on the amount of the compounds present. Two laws describe the absorbed radiations and the concentration of the compound:

- **Beer's law:** states that "the absorption of radiation by a given thickness of a solution, of a given concentration, is the same as that of twice the thickness of a solution, of half concentration".
- **Bouguer's or Lambert's law:** states that "each layer of equal thickness absorbs an equal fraction of radiation which passes through it".

Measurement of oxygen saturation depends on the observation that oxygenated Hb (oxy-Hb) and reduced Hb (deoxy-Hb) differ in their absorption of red and infrared light.

N.B.: In Blood Gas Analyzers, oxygen saturation is measured by the same technique where the blood sample is drawn up into the apparatus by a system of pumps, to be diluted and hemolysed before entering the cuvette. Light passes through a filter to provide a monochromatic beam i.e., of a single wavelength, and this light passes through the cuvette of hemolysed blood and is then detected by a photocell.

In Pulse Oximetry, the pulse oximeter probe consists of (figure 7-65):



Figure 7-65: A pulse oximeter (left) and a portable mini-pulse oximeter (right)

- A photosensor containing a light source (2 light-emitting diodes) present on one side emitting **660 and 940 nm** light waves (figure 7-66). The number of wavelengths used must be equal or greater than the number of Hb species present. In pulse oximetry, because 2 types of hemoglobin are tested, at least two different wavelengths are used.

The specific wavelengths chosen depend on the type of the compounds to be measured. In oximetry, 660 and 940 nm wavelengths are chosen because oxy- and deoxy-hemoglobin differ maximally in their absorption at these wavelengths.

- A photodetector (a photodiode) is present on the other side of the probe.

The probe is placed across trans-illuminated tissues as fingers, toes, ear lobes or nasal bridges (i.e., **transmission spectrophotometry**).

- At wavelength 660 nm (which corresponds to the red region of the light spectrum); reduced Hb absorbs more light than oxy-Hb (or oxy-Hb reflects more red light than reduced Hb). Therefore, oxy-Hb appears red to the naked eye while reduced or deoxy-Hb appears blue or cyanotic to the naked eye.

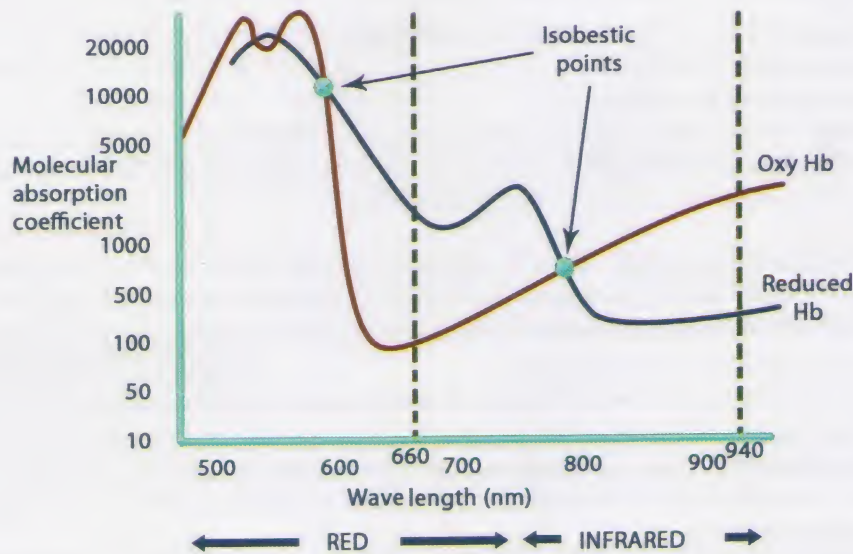


Figure 7-66: Spectrophotometry

- At wavelength 940 nm (which corresponds to the infrared region of the light spectrum); oxy-Hb absorbs more infrared light than reduced Hb. Therefore, the change in light absorption during arterial pulsation is the basis of oximetry.
- The ratio of the absorption at the red and infrared wavelengths is analyzed by a microprocessor to give O_2 saturation (SpO_2) of arterial pulsations only.

$$\% \text{ Saturation} = \frac{\text{Oxy-Hb}}{\text{Oxy-Hb} + \text{Deoxy-Hb}} \times 100$$

N.B.: At the isobestic point, absorption is identical for both types of Hb; the specific wavelengths chosen should be away from the isobestic points.

B- Optical Plethysmography Principle:

It is used to identify arterial pulsations only. With each pulse of arterial blood, the probe site (e.g., fingertip) increases in volume, the path length of light increases, and the absorbance of light at 660 nm and 940 nm increases. This pulse-added absorbance is considered to be due to the pulsatile flow of arterial blood at the probe site. This is performed by a microprocessor to avoid measuring the O_2 saturation of the non-pulsating blood of veins and tissues. Therefore, the resulting pulse oximeter saturation is called SpO_2 (p = pulse-added absorbance) which belongs to pulsating blood only (it is arterial in most cases).

N.B.: **Recently**, a completely new approach (by Masimo company) to analysis of the oximeter light absorbance signals using **adaptive digital filtering** is used, which greatly decreases motion artifacts. This technology uses **8 wavelengths** of light, similar to co-oximeters. It can measure carboxy-Hb, met-Hb, and other parameters such as fractional saturation and total Hb saturation non-invasively (figure 7-67).



Figure 7-67: A Masimo pulse oximeter

Disadvantages:

1- Accuracy:

- It is accurate from $\pm 2\%$ to $\pm 6\%$ when SaO_2 ranges from 80-100%.

It is inaccurate at low SaO_2 ($< 70\%$).

- The accuracy is increased by addition of:
 - Plethysmography principles: to detect arterial pulsation. Therefore, it detects O_2 saturation in arterial blood only and avoids measuring O_2 saturation of non-pulsating blood of veins and tissues.
 - ECG signals to increase the accuracy of pulse detection.

2- Clinical Sensitivity:

- Because the **oxy-Hb dissociation curve** is **sigmoid shaped**, there may be a significant decrease in arterial O_2 tension (PaO_2) before Hb saturation begins to decrease i.e., large changes in PaO_2 above 75 mmHg are associated with small changes in saturation and small changes in PaO_2 below 75 mmHg are associated with large changes in Hb saturation.

That means, pulse oximetry gives **no indication of early trends in PaO_2** during anesthesia with **elevated FiO_2** because when PaO_2 is > 90 mmHg, SaO_2 is nearly 100% and almost independent of PaO_2 . Therefore,

- Only gross abnormalities are detectable in most anesthetized patients. Endobronchial intubation (usually gives enough PaO_2) is not detected by pulse oximeter in absence of lung disease or low inspired O_2 concentrations.
- A saturation of 94% corresponds to a PaO_2 of 75 mm Hg, so the lower alarm limit of the pulse oximeter device should be set at this point (i.e., 94%). Some clinicians, make the lower alarm limit of the pulse oximeter device at 90 % which corresponds to a PaO_2 of 60 mmHg.

At 80% saturation, clinically detectable cyanosis occurs (which requires 5 g of deoxy-Hb).

3- Interference: it decreases the accuracy.

a- Intrinsic:

- **Carboxy-Hb (CO-Hb)** as in carbon monoxide poisoning:

CO-Hb has the **same absorption coefficient of oxy-Hb**. It absorbs light at a wave-length of 660 nm, which corresponds to the red light spectrum i.e., it is identical to oxy-Hb. Therefore, it gives **false high SaO_2** (i.e., CO-Hb is misinterpreted as being oxy-Hb).

- **Met-hemoglobinemia (Met-Hb):**

Met-Hb has the **same absorption coefficient of both oxy-Hb and deoxy-Hb**. It absorbs light at a wavelength 660 and 940 nm which corresponds to the red and infrared light spectrum respectively i.e., it is identical to oxy-Hb and deoxy-Hb. Therefore, a 1: 1 absorption ratio occurs and **SaO_2 becomes around 85%**. Therefore, if the actual SaO_2 is $< 85\%$, a false high reading occurs (as met-Hb is misinterpreted as oxy-Hb) and if the actual SaO_2 is $> 85\%$, a false low reading occurs (as met-Hb is misinterpreted as deoxy-Hb).

The best way to differentiate is by co-oximeter for functional and fractional saturation (see later).

- **Intravenous dyes: methylene blue and indocyanine green** has the **same absorption coefficient of deoxy-Hb**. They absorb light at a wavelength of 660 nm, which corresponds to red light spectrum i.e. they are identical to deoxy-Hb. Therefore, **false low SaO_2** occurs (i.e., both methylene blue and indocyanine green are interpreted as being deoxy-Hb).

N.B.: - Bilirubin and fetal Hb (Hb-F) produce little interference with SaO_2 measurement.

- Pigmented skin does not affect SaO_2 measurement; so, the pulse oximeter is valuable in patients of African or Asian origin, in whom hypoxia is more difficult to detect clinically.

b- Extrinsic:

- **Patient motion** such as shivering or moving the finger. It is avoided in recent technology-pulse oximeters.
- **Electrocautery** interference.
- **Excessive ambient light as fluorescent room lights**. They can interfere with pulse oximeter especially during excessive vasoconstriction i.e., decreased pulse amplitude.
- **Finger nail polish** - Red has no effect.
 - Dark colors as blue, black, or green produce false low SaO_2 by 3-5%.
- **Probe mal-position (Penumbra effect)**: As during gradual withdrawal of the probe from the finger, SaO_2 reading remains present. Therefore, when the patient is hypoxic, the pulse oximeter can not detect hypoxia as it gives the last SaO_2 figure. But when the probe is withdrawn more from the finger the device gives an alarm (probe off the patient), which occurs late after the patient has been hypoxic for a long time. This is known as the Penumbra effect which is done to decrease the signal-to- noise ratio.

- **Finger nail bed infection** (onychomycosis) produces false low SaO_2 by 3-5%.
- **Venous pulsation in a dependent limb** e.g., in tricuspid incompetence produces false low SaO_2 because the pulse oximeter will read venous saturation as arterial saturation.
- **Low perfusions** e.g., - low cardiac output,
 - very low Hb ($< 5 \text{ g/dL}$),
 - Raynaud's disease,
 - hypothermia which causes excessive vasoconstriction,
 - and - increased systemic vascular resistance.

4- Complications of Pulse Oximetry:

Heat from the light source or sensor pressure may rarely produce tissue damage especially in neonates and if the monitor is left in the same site for a long time and not periodically removed. Nowadays, there are special probes designed for neonates and children to avoid excessive pressure on their fingers.

Other Types of Oximeters:

1- Co-Oximeter (Hemoximeter):

- It is a **transmission oximetry**. It is **in vitro** oximetry capable of transmitting **4-6 or more wavelengths** of light through a blood sample. It is capable of detection of oxy-Hb, deoxy-Hb, CO-Hb, met-Hb, and other dys-Hb as sulf-Hb.

$$\text{Fractional saturation (HbO}_2\%) = \frac{\text{Oxy-Hb}}{[\text{Oxy-Hb} + \text{deoxy-Hb} + \text{CO-Hb} + \text{met-Hb}]} = \frac{\text{Oxy-Hb}}{\text{Total Hb}}$$

$$\text{Functional saturation (SaO}_2\%) = \frac{\text{Oxy-Hb}}{[\text{Oxy-Hb} + \text{deoxy-Hb}]}$$

Note that dys-Hb is absent from the denominator.

2- Intravascular Oximeter:

Idea:

It allows **continuous monitoring of O_2 saturation** of the blood inside a blood vessel through a catheter containing **fiberoptic bundles** that can transmit light of **3 wavelengths** to and from the catheter tip. It is a **reflection spectrophotometry** and not a transmission spectrophotometry.

Fibrin deposition at the tip of the catheter may interfere with the measurement; therefore, a continuous flush of heparinized saline may be needed.

Uses:

- If the fiberoptic sensor is placed in **the internal jugular vein**, it measures jugular bulb O_2 saturation, so it can assess the adequacy of **cerebral O_2 delivery** e.g., during carotid endarterectomy.
- If it is placed in the **supra-hepatic vein**, measurement of hepatic O_2 saturation is available, so it can assess adequacy of **hepatic O_2 delivery** e.g., during hepatic surgery.
- **Mixed venous oximeters (pulmonary artery oximetry)** where the fiberoptic bundles which transmit the 3 wavelengths are present in a specialized pulmonary artery catheter. The tip of the catheter containing the fiberoptic bundles can measure the O_2 saturation in the mixed venous blood ($\text{S}\bar{\text{v}}\text{O}_2$) in pulmonary artery.

Q: Discuss pulmonary artery oximetry?

A: Discuss the following items: - Physiology of O_2 transport.

- Principles of action of pulse oximetry.
- Factors that increase or decrease $\text{S}\bar{\text{v}}\text{O}_2$ "see before".

3- Cerebral Oximeter (Near-Infrared Spectroscopy):

Idea:

- It monitors **regional O_2 saturation of Hb in the brain (rSO_2)**. A sensor is placed over the forehead and emits **two lights of specific wave-lengths** of near-infrared spectrum (730 and 810 nm). It measures light reflected back to the sensor (near-infrared spectroscopy) (i.e., **reflection spectroscopy**).

Cerebral oximetry measures venous and capillary blood O_2 saturation in addition to arterial blood O_2 saturation (unlike pulse oximetry). Therefore, it measures the average O_2 saturation of all regional microvascular Hb (figure 7-68). The contribution of cerebral arterial and venous blood is in a ratio of 25: 75 with the contribution of capillary blood felt to be negligible.

Other devices are used mainly in neonates and infants because they have thin skulls and small heads where light can be transmitted through one side of the head and detected on the other side i.e., transmission spectroscopy.

Normal cerebral rSO_2 values range from 55-75%.

Values $< 50\%$ for long periods of time and below 40% for short periods of time or change of more than 20% from baseline, are associated with an increased incidence of neurological complications.



Figure 7-68: Cerebral oximeter

Uses:

- During labor as a fetal monitor and after labor to detect cerebral edema in the newborn.
- Dramatic decrease in rSO_2 occurs in: - cardiac arrest, - cerebral embolization, - deep hypothermia, and - severe hypoxemia.

Disadvantages: Its results are affected by inter-individual variations, extracranial blood contamination, ambient light, probe positioning, and sample volume inaccuracies (increased signal path during cerebral edema following head injury).

Fiberoptic O_2 Sensor (Optode) Fluorescence-Based Blood-Gas Analysis

It enables continuous invasive arterial blood gases analysis.

Idea:

It is based on **fluorescence quenching**.

The probe is inserted through an 18- or 20- standard wire gauge radial artery catheter. The probe is formed of (figure 7-69):

- A light source which is a **pulsed xenon lamp**. The light is transmitted by a fiberoptic bundle to the tip of the probe.
- A **hydrophilic matrix** which is attached directly to the end of the probe. A **fluorescent weak acid dye** is bonded (attached) to the matrix which is embedded in the blood to be tested.
- A **silicone capsule** containing a **buffer** is present at the tip of the probe. The buffer is at equilibrium with the CO_2 tension of the blood. There is also **another oxygen-quenchable dye** which is dissolved in the silicone.
- A **sensor** which detects the emitted light from the blood sample which is transmitted to the device through a fiberoptic bundle.

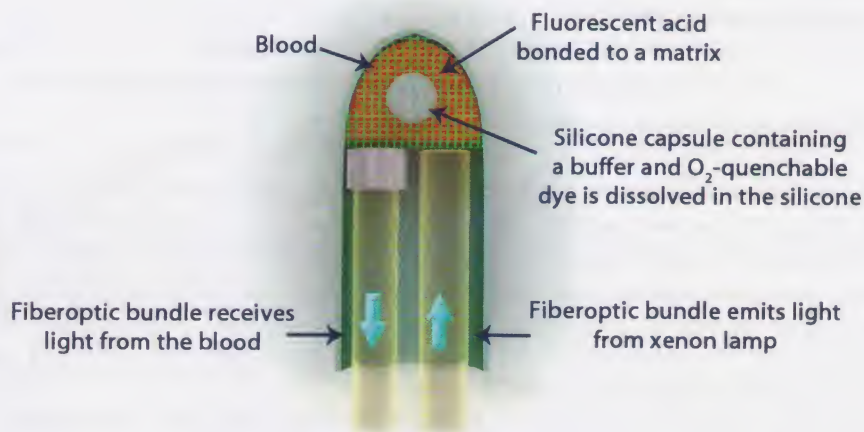


Figure 7-69: Optode

The Method of Measurement:

High energy light from the xenon lamp is transmitted to the tip containing **fluorescent dyes**. These fluorescent dyes are **excited by the light**. The dyes **return to their original states** with **emitting a light of specific wavelength and intensity** which depends on O_2 , CO_2 , and H^+ concentrations. O_2 , CO_2 , and H^+ ions can **reduce "quench or absorb" energy from the emitted light**; therefore, the intensity of light emitted from the fluorescent dyes is **reduced**. The **sensor** can detect the **reduction of the emitted fluorescent light** which is **directly proportional to the concentration** of O_2 , CO_2 , and H^+ ions.

Uses:

Nowadays, it is **used to measure the viability of tissue grafts and surgical flaps**.

Advantages:

- 1- It is accurate (98%) when compared with a blood gas analysis of the withdrawn samples.
- 2- It does not affect blood withdrawal or invasive blood pressure measurement through the arterial catheter.
- 3- The sensor is coated with bonded heparin to decrease the thrombogenicity. The heparin is non-toxic and non-hemolytic.

Disadvantages:

- 1- There is interference from N_2O and halothane which give a false high PO_2 values.
- 2- It needs frequent calibration.
- 3- It is expensive and disposable for a single use up to 72 hours only.

Transcutaneous O_2 Tension Measurement ($PtcO_2$)

It enables a **continuous non-invasive measurement** of PO_2 .

Idea:

- A **modified Clark O_2 electrode** with platinum cathode, silver anode, and electrolyte (retained by a membrane) is heated by a heater (ideally to $\geq 43^\circ C$) and then placed on the surface of the skin as a surface electrode (figure 7-70). The skin temperature is measured by a thermistor, and this is used to control the heater power.
- **Surface heating** causes:
 - Vasodilatation of the capillary bed i.e., local hyperemia with arterialization of blood; therefore, the oxygen used by the skin becomes negligible compared with the total oxygen present in the vasodilated hyperemic capillaries.
 - Facilitation of O_2 diffusion through the stratum corneum.
 - Shifting of oxy-Hb dissociation curve to the right.
- O_2 diffuses from the arterialized capillary loop (dermal) through stratum corneum and the partial pressure is measured by the surface electrode (reflecting PaO_2). The value obtained is called $PtcO_2$.
- In neonates, the amount of O_2 utilized by stratum corneum is nearly cancelled and $PtcO_2$ is roughly = PaO_2 .

In adults, the stratum corneum is thicker and utilizes more O_2 ; therefore, $PtcO_2$ is $< PaO_2$.

Transcutaneous index = $PtcO_2 / PaO_2$

Average values: Neonates 1.0
 Pediatrics 0.9
 Adults 0.8
 Elderly patients 0.6-0.7

- A combined electrode is available which allows simultaneous measurement of PO_2 and PCO_2 .

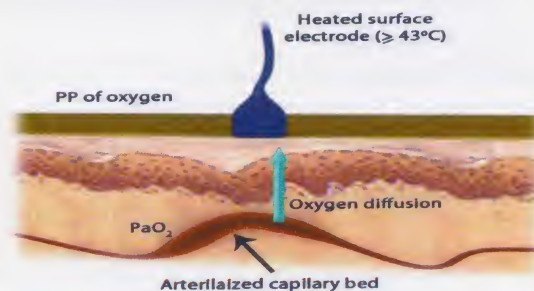


Figure 7-70: Transcutaneous O_2 tension measurement (PP = partial pressure)

Uses: It is used in pediatric intensive care units especially in neonates and infants. It is now replaced by the pulse oximetry.

Advantages:

Transcutaneous O₂ electrode is superior to pulse oximetry in patients with carbon monoxide poisoning because it continues to measure O₂ tension accurately.

Disadvantages:

- 1- It needs a **warm-up time** of 10-15 minutes.
- 2- It has a **slow response time** where the electrode responds in about **1 min** to changes of oxygen tension at its surface. Unfortunately, the changes in cutaneous oxygen tension occur after the changes in arterial blood tension; therefore, the result is delayed.
- 3- It needs regular **calibration** before each application to the skin.
- 4- There is a risk of **skin burns** especially in neonates (particularly at a temperature of 45 °C for > 4 hours). This occurs when the thermistor fails to control the temperature. Therefore, a second thermistor should be present to switch the heater off if the primary heating circuit fails. The electrode position should be changed routinely every 3-6 hours to ensure safety.
- 5- It gives **variable results** in the same patient, from site to site (peripheral versus central location of the sensor), and in different age groups (as above).
- 6- **The sensor's membrane and electrolyte** of miniature Clark's electrode must be **changed and replaced periodically**.
- 7- It is unreliable in the following conditions:
 - Low cardiac output.
 - Skin hypoperfusion.
 - Peripheral vasoconstriction.
 - Hypocapnia.
 - Halothane anesthesia because halothane can be reduced electrochemically giving false high reading.

Actually, PtcO₂ follows changes in O₂ delivery (i.e., CO × CaO₂) especially in hypovolemic patients. Therefore, PtcO₂ monitors O₂ delivery in the tissues rather than CaO₂. When PtcO₂ is normal or high, this indicates that tissues are well oxygenated. When PtcO₂ is low, this indicates either decreased PaO₂ or decreased tissue blood flow.

8- It is **less accurate** (than blood sample analysis) due to:

- O₂ metabolism during diffusion via the skin,
- shift in O₂ dissociation curve with temperature,

and - edema produced by heating which decreases skin perfusion especially with high temperatures.

Conjunctival O₂ Tension Measurement (PcjO₂)

It consists of a Clark O₂ electrode which rests against the conjunctiva.

Advantages:

- It does **not require heating** due to the very thin epithelium of the conjunctiva (2-4 cells thick).
- It has a **more rapid response time** as it equilibrates within 60 seconds due to the dense conjunctival capillaries.
- It reflects PaO₂ in the internal carotid artery and hence O₂ delivery to the brain.

Disadvantages:

- Lower reading values than PaO₂ (trans-conjunctival index or PcjO₂ / PaO₂ = 0.5-0.8 i.e., 50-80%).
- Like PtcO₂, measured values are affected by age, cardiac output, halothane and hypovolemia.

N.B: O₂ Sensors: include • Fuel cell (galvanic O₂ analyzer).

- Clark polaro-graphic electrode (O₂ electrode).
- Paramagnetic analyzer.
- Fiberoptic O₂ sensor.
- Transcutaneous O₂ sensor.
- Conjunctival O₂ sensor.

Gastric Intra-luminal Tonometry

It measures intra-mucosal pH of gastric mucosa (an indirect measurement) to detect **splanchnic tissue acidosis** which is an early sign of **splanchnic hypoperfusion during shock**.

Idea:

- Intra-luminal PCO₂ is equivalent to the PCO₂ in the gastric mucosa, and the concentration of intra-mucosal HCO₃⁻ is equivalent to that in arterial blood.

- The **nasogastric silastic tonometry balloon** which is permeable to CO_2 is filled with saline or air and is placed in the stomach.
- Splanchnic hypoperfusion causes tissue acidosis which increases the concentration of intra-mucosal CO_2 and PCO_2 . Over a period of time, CO_2 diffuses from the gastric wall to the gastric lumen and equilibrates with the silastic balloon (figure 7-71); therefore, the CO_2 pressure within the balloon equilibrates with that in the lumen of the stomach and, in turn, with the pressure in the gastric mucosal cells. The CO_2 tension in the samples withdrawn from the balloon is measured.
- By measuring the arterial HCO_3^- concentration and utilizing **Henderson-Hasselbalch equation**, the intra-mucosal pH can be calculated as follows:

$$\text{pHi} = 6.1 + \text{Log} \frac{[\text{HCO}_3^-]}{0.03 \text{ PCO}_2}$$

Where: 6.1 = pKa of H_2CO_3 system.

$[\text{HCO}_3^-]$ = Arterial plasma HCO_3^- concentration.

PCO_2 = CO_2 tension of saline in the balloon.

0.03 = Solubility coefficient of CO_2 .

Values below 7.2-7.32 indicate intracellular acidosis, reflecting inadequate oxygen delivery.

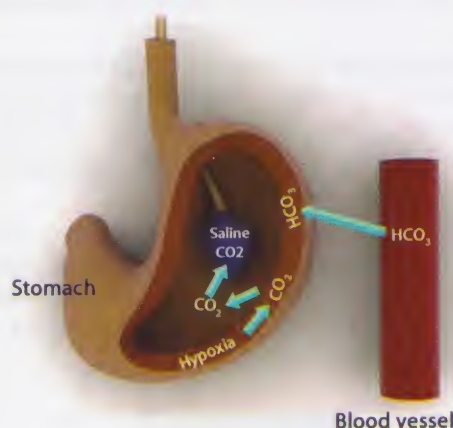


Figure 7-71: Gastric intra-luminal tonometry

VI- CO_2 Monitoring

It includes:

- CO_2 excretion in expired gas: by - capnography,
- gas chromatography,
and - mass spectrometry.
- CO_2 excretion in tissues (PCO_2): by - Astrup interpolation technique,
- Severinghaus CO_2 electrode,
and - transcutaneous partial pressure of CO_2 .

N.B.: **Astrup interpolation technique** is an indirect method of estimating PCO_2 . It has been used until 1970, but is obsolete nowadays. This technique is based on the linear relationship between pH and log PCO_2 over the physiological range using a **Siggaard-Anderson nomogram**.

End-Tidal CO_2 (ET CO_2) Analysis (Capnography) (Infrared Analyzer)

It enables continuous measurement of CO_2 concentration in a gas mixture.

Principles: Infrared absorption spectrophotometry.

It is used for gases that have 2 or more different atoms e.g., CO_2 or N_2O (not O_2) because they can absorb infrared radiation (CO_2 absorbs light strongly at 4280 nm). By measuring the fraction of radiation absorbed by a gas mixture, the partial pressure of a particular gas can be determined as each gas absorbs infrared radiation at a specific wavelength (figure 7-72). It consists of:

- An **infrared source** emitting radiation with a specific frequency. It is chosen by **filters** which are suitable for the expected gases in the mixture. If the infrared analyzer is used to measure multiple gases, many wavelengths are allowed to pass by special filters according to the gas measured. In capnography, one wavelength (4280 nm) is allowed to pass.

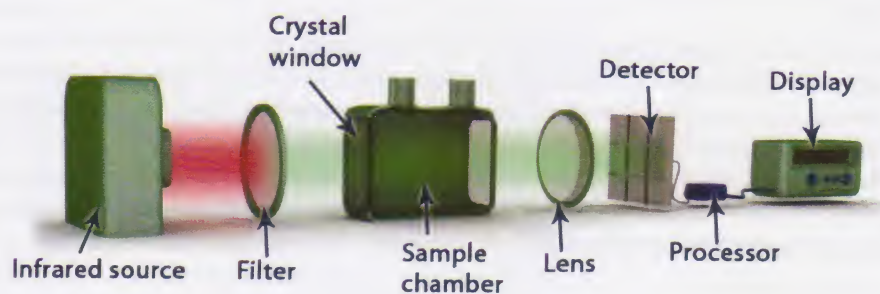


Figure 7-72: Infrared absorption spectrophotometry

- The radiation enters a **sample chamber** that has windows made of materials allowing infrared radiation to pass through e.g., **NaCl, silver bromide, or sapphire**.
 - Then radiation falls on the photo-detector, so the greater the absorption of infrared radiation by the gas, the less radiation monitored by the detector. The output is electronically processed to indicate the concentration of the gas.
 - A 2nd beam of radiation from the same source passes through the reference cell containing CO₂ free gas. The output is used as a reference to the 1st beam to increase accuracy (**a double beam analyzer**), because changes of outputs which are not due to changes of CO₂ concentration in the sample cell also appear at a reference detector and may be subtracted from the outputs of the sample detector.
- The sample is taken by 2 types of capnography:

a- Mainstream (Flow Through or Non-Diverting Type):

A special connector is needed in the breathing system which incorporates a channel with the sapphire windows. The analyzer sits over this channel and the infrared beam passes directly through the gases in the airway. Therefore, there is no sample line and the transit time is nil (i.e., rapid response time). There is also a portable mainstream model (figure 7-73).



Figure 7-73: A mainstream portable capnogram

Disadvantages:

- It is **bulky**, so it may cause traction on the endotracheal tube.
- It needs sterilization between cases.
- It produces **radiant heat**, so skin burns may occur (new designs avoid this).
- Old models do **self zeroing during inspiration**, so they can not detect inspired CO₂ which is important for breathing system malfunction e.g., expiratory or inspiratory valve malfunction, exhausted CO₂ absorbent, or rebreathing.

b- Side Stream (Aspiration or Diverting Type):

It continuously sucks gas from the breathing circuit into a sample cell within the monitor by a narrow catheter (150-250 mL/min). There is a moisture trap and an exhaust port.

Disadvantages:

- There is a **transit time**, but with high aspiration rates and low dead space sampling tubing, transit time and response time are decreased to < 1 sec.
- **Continuous aspiration of anesthetic gas** represents a **leak** in the breathing circuit which can contaminate the operating room unless it is scavenged or returned to the breathing system.
- In pediatrics, as a small tidal volume is present, high rates of aspiration may entrain fresh gas from the circuit and **dilute end tidal CO₂**.
- **Calibration is needed** using a source of known CO₂ concentration (usually 5%).

- The narrow tube is **easily obstructed by water vapor**.
- It detects inspired CO_2 ; therefore, expiratory valve malfunction and exhausted CO_2 absorbent can be detected by presence of CO_2 in inspired gas, but in inspiratory valve malfunction, although it causes rebreathing of CO_2 , this is not apparent because part of the inspiratory volume will still be free of CO_2 . Therefore, the monitor will read zero during that part of inspiration. It can be detected only by comparing the time of expiration in the trace with the inspiration: expiration (I: E) ratio where the expiration time in the trace appears to be longer than the actual I: E ratio adjusted in the mechanical ventilator.

Indications:

- 1- It is **essential** in all anesthetized patients because:
 - It confirms adequate ventilation.
 - It detects esophageal intubation (the most reliable sign).
- 2- It allows maintaining **normocapnia for adequate cerebral perfusion** in:
 - Intracranial hypertension.
 - Carotid artery surgery.
- 3- It can be used for diagnosis of **air embolism** (causing rapid fall of CO_2) as in sitting craniotomy. See below for the other values of capnography.

Normal CO_2 Waveform

Phase I: indicates the dead space (both mechanical and anatomical). No CO_2 is present.

Phase II: indicates a mixture of dead space and alveolar gas.

Phase III: indicates the alveolar gas. It is normally plateau in shape.

Phase IV: This is the inspiratory down-stroke. It normally reads zero (CO_2 -free inspired gas) (figure 7-74).

" α " angle: is the angle between the upstroke of phase II and the plateau of phase III.

" β " angle: is the angle between phase III and IV.

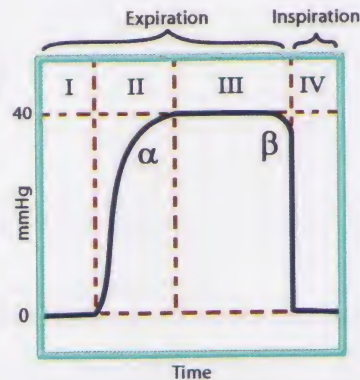


Figure 7-74: Normal CO_2 Waveform

- Normal values of:**
- End-tidal CO_2 tension (P_{ETCO_2}) = 35 mmHg (2-5 mmHg less than the arterial CO_2).
 - Arterial CO_2 tension (P_{aCO_2}) = 40 mmHg.
 - Mixed venous CO_2 tension = 45 mmHg (5 mmHg more than the arterial CO_2).

Values: The shape of CO_2 waveform can reveal the following:

1- A Sudden Cessation of End-Tidal CO_2 Waveform indicates:

- circuit disconnection,
- or • cardiac arrest.

2- The CO_2 Level:

Increased CO_2 Values (elevated expiratory plateau) indicate:

- incorrect calibration,
- or • any cause of hypercarbia e.g., inadequate ventilation or malignant hyperthermia ($\text{ETCO}_2 > 50$ mmHg).

Decreased CO_2 Values (decreased expiratory plateau) indicate:

- incorrect calibration,
- any cause of hypocarbia e.g., hyperventilation or hypothermia,
- or • increased $P_{\text{a}}-P_{\text{A}}$ (increased $P_{\text{a}}-P_{\text{ETCO}_2}$ gradient "see later").

Decreased End-Tidal CO₂ (ET CO₂) with Increased P_a-P_A (or Increased P_a-P_{ET}CO₂) Gradient:

This indicates **ventilation/perfusion (V/Q) mismatching (decreased lung perfusion)**. Normally, P_{ET}CO₂ or P_ACO₂ is less than P_aCO₂ by 2-5 mm Hg. This gradient reflects alveolar dead space i.e. alveoli that are ventilated, but not perfused. So, decreased lung perfusion e.g., air embolism, upright position, decreased cardiac output and decreased arterial blood pressure, increases alveolar dead space. The increased alveolar dead space dilutes expired CO₂ and decreases CO₂ excretion causing decreased end-tidal CO₂ (ET CO₂). This increases the gradient between P_{ET}CO₂ and P_aCO₂ which may reach 20-30 mmHg.

3- An Increase in the "α" Angle and Slope of Phase III or Even Absence of Phase III (i.e., no plateau) i.e., prolonged expiratory upstroke indicates:

- chronic obstructive airway diseases,
- bronchospasm,

or • mechanical obstruction to exhalation (figure 7-75).

In these previous conditions, the severity of the obstruction is inversely related to the rate of rise of endotracheal CO₂ i.e., more slope = more obstruction. The well ventilated areas of the lung tend to empty early in expiration whilst poorly ventilated areas empty late, thus causing an upwardly sloping alveolar plateau.

The angle and the slope decrease with treatment of the bronchospasm or relief of the mechanical obstruction.

4- Depression during Phase III (figure 7-76) indicates:

- spontaneous respiratory efforts,
- and • a curare cleft (incomplete paralysis).

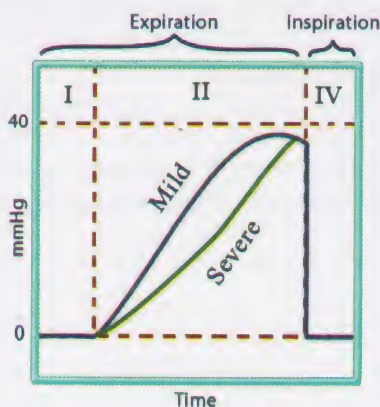


Figure 7-75: Absence of phase III

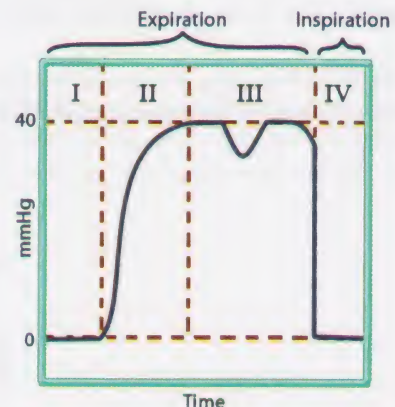


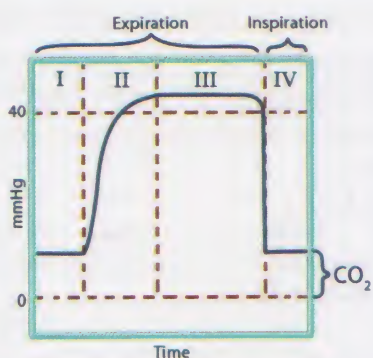
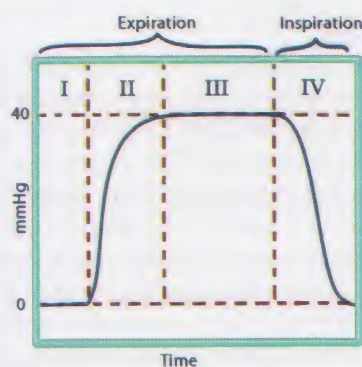
Figure 7-76: Depression during phase III

5- Failure of the Inspired CO₂ to Return to Zero (i.e., CO₂ during all inspiration) or a rise of the base line (figure 7-77) indicates:

- incorrect calibration to zero,
- incompetent expiratory valve,
- failure of CO₂ absorbent (channeling, exhaustion, bypass) i.e., rebreathing,
- and • CO₂ delivery to the breathing system via a fresh gas flow.

6- Persistence of Expired CO₂ during the First Part of the Inspiratory Cycle (i.e., CO₂ during inspiration too) **or Prolonged Inspiratory Downstroke** (figure 7-78) indicates:

- incompetent inspiratory valve,
- inspiratory obstruction to gas flow (e.g., kinked tube),
- and • rebreathing.

Figure 7-77: Failure of CO₂ to return to zeroFigure 7-78: Persistence of expired CO₂ during the first part of the inspiratory cycle

7- Gradual Decrease in CO₂ Waves Until They Disappear Completely (figure 7-79) indicates: **esophageal intubation** as CO₂ that has been insufflated into the stomach during bag-mask ventilation is washed out during esophageal ventilation within a few breaths (usually within 3 tidal volumes).

8- Cardiogenic Oscillations If Synchronized with ECG: indicates: Ventilator pressure relief valve perturbations (figure 7-80).

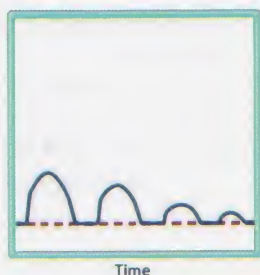
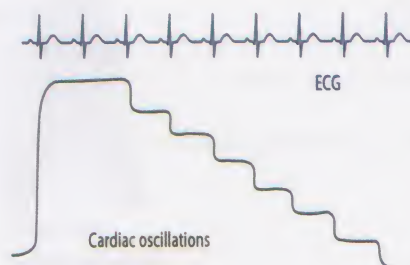
Figure 7-79: CO₂ waveform of esophageal intubation

Figure 7-80: Cardiogenic oscillations

9- Camel Sign or Biphasic-Shaped Wave (figure 7-81):

This occurs in a patient with a **single transplanted lung** because **the differences** in the compliance and expiratory flow rates of a **native and transplanted lung** after single lung transplant ion for emphysema cause alterations in **intraoperative capnography**. Therefore, a **biphasic pattern** of CO₂ exhalation is produced, with the first peak reflecting exhalation from the transplanted lung, and the 2nd peak exhalation from the native lung.

10- Spontaneous Respiration:



Figure 7-81: Camel sign or biphasic waveform

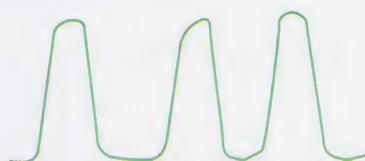


Figure 7-xxxx: Spontaneous Respiration

11- During Cardio-Pulmonary Resuscitation (CPR):

Patients with cardiopulmonary arrest or low perfusion states, and patients with respiratory stress have lack of circulation; therefore, no CO₂ trace occurs (they should be differentiated from esophageal intubation), but on return of spontaneous circulation, there is increased exhaled CO₂ due to increased

pulmonary blood flow. During CPR, this sign can be used to indicate the **prognosis or the efficacy of resuscitation**.

- If there is **exhaled $\text{CO}_2 > 10\text{-}15 \text{ mmHg}$** , patients are likely to be resuscitated i.e., mostly there is a **good prognosis or adequate cardiopulmonary resuscitation (CPR)**, so continuation of CPR is useful.
- If there is **exhaled $\text{CO}_2 < 10\text{-}15 \text{ mmHg}$** , patients are unlikely to be resuscitated i.e., mostly there is a **bad prognosis or inadequate CPR**, so continuation of CPR is not useful.

The Arterial-Alveolar Difference in CO_2 ($\text{PaCO}_2\text{-PACO}_2$):

- End-tidal CO_2 tension (P_{ETCO_2}) is the tension of CO_2 in the exhaled gas at the end of exhalation. Because this gas originates from the alveoli, it is **considered to represent the CO_2 tension in the alveolar gas (PACO_2)**; therefore, ($\text{PaCO}_2\text{-PACO}_2$) is usually **expressed as ($\text{PaCO}_2\text{-P}_{\text{ETCO}_2}$)**.
- **In ideal alveoli**, where ventilation and perfusion are perfectly matched, the PACO_2 is nearly the same as CO_2 in arterial blood (PaCO_2) and the $\text{PaCO}_2\text{-PACO}_2$ difference is zero i.e., PACO_2 is used as a **measure for alveolar tidal volume**.
- **In alveolar dead space**, i.e., alveoli that are ventilated, but not perfused, **ET CO_2 concentration is the same as inspired CO_2 (P_iCO_2)**. As normally alveolar dead space is absent, P_iCO_2 is normally zero.
- Because the end-tidal CO_2 (P_{ETCO_2}) comprises gas from both ideal alveoli and dead space alveoli (i.e., ventilated alveoli, but unperfused), the ($\text{PaCO}_2\text{-P}_{\text{ETCO}_2}$) gradient is used as a **measure of alveolar dead space ventilation** (figure 7-82).

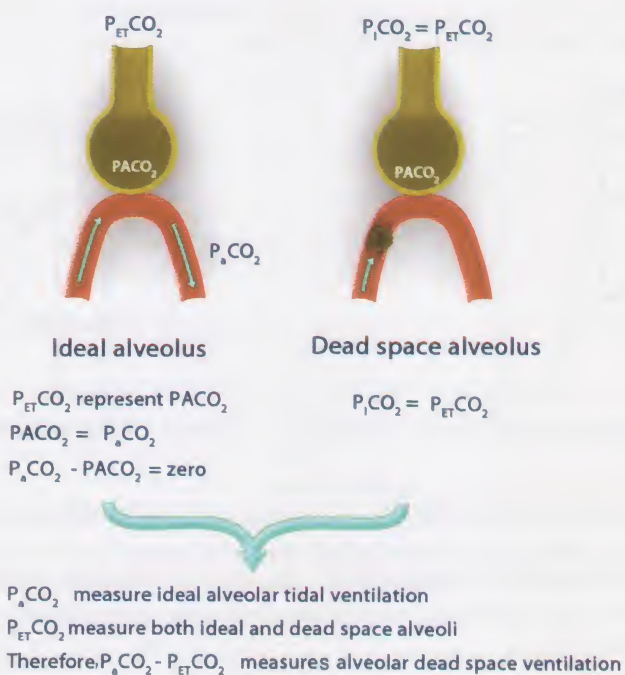


Figure 7-82: P_{ETCO_2} in ideal and dead space alveoli

- For example, in normal conditions: tidal volume = 500 mL,
anatomical dead space = 150 mL,
 $\text{PaCO}_2 = 40 \text{ mm Hg}$,
 $\text{P}_{\text{ETCO}_2} = 36 \text{ mm Hg}$.

Therefore, alveolar tidal volume = $500 - 150 = 350 \text{ mL}$.

$$\text{Ratio of } \frac{\text{Alveolar deadspace (V}_D\text{)}}{\text{Alveolar tidal volume (V}_T\text{)}} = \frac{\text{PaCO}_2 - \text{P}_{\text{ETCO}_2}}{\text{PaCO}_2} = \frac{40 - 36}{40} = 10\%$$

Therefore, $350 \text{ mL} \times 10\% = 35 \text{ mL}$ wasted ventilation from each alveolar tidal volume (to some alveoli not perfused).

The ideal alveolar ventilation = $350 - 35 = 315 \text{ mL/breath}$.

This ratio is increased in conditions such as pulmonary embolism or low cardiac output states where the dead space alveoli are increased and is useful during weaning of mechanical ventilation.

- Physiological dead space = anatomic dead space + alveolar dead space

$$= 150 + 35 = 185 \text{ mL/breath.}$$

$$\frac{\text{Physiological deadspace}}{\text{Tidal volume}} = \frac{185}{500} = 37\%$$

- As $(\text{PaCO}_2 - \text{P}_{\text{ETCO}_2}) = 2\text{-}5 \text{ mm Hg}$

Therefore, P_{ETCO_2} is only used as a noninvasive estimation of PaCO_2 , but to get the actual PaCO_2 which is important in some conditions such as mechanical ventilation or during neurosurgical anesthesia, only an arterial blood sample is used.

Enghoff modification of Bohr's equation (modified Bohr equation) is discussed later with pulmonary function tests.

N.B.: The mixed expired CO_2 fraction or partial pressure ($\text{P}_{\text{E}}\text{CO}_2$) is usually determined from collection of expired gas for several minutes. This should be distinguished from P_{ETCO_2} sampled at the end of a single breath.

Severinghaus CO_2 Electrode

It enables an indirect method of CO_2 measurement from H^+ change in a blood sample (mainly) or a gas mixture. It is the probe present in the blood gas analyzer machine.

Idea:

- CO_2 reacts with water to produce H^+ ions by a reversible reaction



At 1st the reaction gives carbonic acid which in turn, dissociates to produce H^+ ions and bicarbonate ions; therefore, CO_2 tension is related to H^+ ion concentration.

- The apparatus incorporates H^+ ion sensitive glass shown in the centre with an electrode on either side of it (figure 7-83).

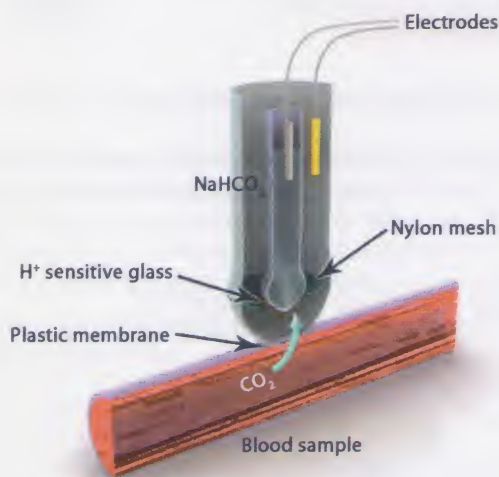


Figure 7-83: Severinghaus electrode

This glass is in contact with a thin film of NaHCO_3 solution in a nylon mesh which is fixed over the glass tip by an O-ring.

- The liquid to be tested, usually arterial blood (also a gas sample can be tested), is separated from the nylon mesh and HCO_3^- by a plastic membrane that is permeable to CO_2 and also is attached by an O-ring.

- At the tip of electrode, CO_2 diffuses via the plastic membrane into the mesh impregnated with HCO_3^- solution and combines with the water present as described above. The resulting change of H^+ concentration is measured by the glass electrode.

New techniques allow electrodes to be fixed on intravenous catheters and produce continuous PCO_2 measurement.

Disadvantages:

- 1- If there is a small **hole in the plastic membrane**, loss of semi-permeability for CO₂ occurs and the device becomes inaccurate.
- 2- The **response time** is 2-3 minutes, slower than H⁺ electrode because CO₂ requires time to diffuse through the plastic membrane.
- 3- As in H⁺ electrodes (see later), **temperature control at 37 °C** is important.
- 4- **Calibration** with a standard gas mixture containing a known concentration of CO₂ is necessary. The concentration of CO₂ is converted to partial pressure (in kPa or mmHg) as follows:

- Partial pressure of a dry gas = Concentration/100 × Barometric pressure.
- Partial pressure of humidified gas = Concentration/100 × (Barometric pressure - SVP of water).

For example, if 5% CO₂ gas is used to calibrate the machine, the analyzing machine should be adjusted to 35 mmHg because partial pressure in mmHg = $5/100 \times (750 - 47) = 35$ mmHg where the 750 is the barometric pressure and 47 is the saturated vapor pressure of the water.

Transcutaneous Partial Pressure of CO₂ Monitoring (PtcCO₂)

Idea: (is the same as transcutaneous O₂ monitoring).

A sensor containing a CO₂ electrode and a heating element is attached to the skin. A CO₂ electrode measures the change in H⁺ as above. $pH = 0.97 (\text{Log } PCO_2)$

Uses: Especially in pediatric intensive care units.

Disadvantages:

- 1- PtcCO₂ changes much less rapidly than PaCO₂ after apnea making PtcCO₂ less useful as an emergency warning device.
- 2- It has a slow response time (about 5 minutes to 90% response).
- 3- PtcCO₂ is always higher than PaCO₂, but there is a **good correlation** over a wide range of values up to 60 mmHg (8 KPa). PtcCO₂ is 130 % of Pa CO₂.

VII- Anesthetic Gas Analysis**Value:**

- Increased End-tidal nitrogen quantitatively detects air embolism or leakage of air into the breathing system.
- Measurement of volatile agents protects against: - unintentional overdose from vaporizer malfunction, and - unintentional misfilling of vaporizers.
- It can be used for O₂, N₂O, and CO₂ analysis.

Techniques:**1- Gas Chromatography (Gas-Liquid Chromatography):**

Chromatography is a general term for analytical procedures that separate a mixture into its components when the mixture passes through a column, due to the difference in the solubility of different components of the mixture with the material in the column.

Chromatography = to write in color.

Idea:

A gas chromatography is formed of:

- **A stationary phase:** It is the chromatographic **column** which is packed with a support material such as **silica-alumina** in the form of very small particles which is then coated with polyethylene glycol or silicone oil. The column is usually a long coiled glass tube. This gives better separation of the components.
- **A mobile phase:** It is the carrier gas, such as nitrogen, argon, or helium. The carrier gas carries the sample to be tested and passes through the column at a speed which depends on differential solubility between the stationary and the mobile phase i.e., **the components with greater solubility in the stationary phase will be retained for a longer period** than the components with lower solubility which will pass faster and be collected earlier at the detector. This allows the gas mixture (the carrier gas and the sample) to be separated into its components according to their solubility in the stationary phase. As solubility is temperature dependent, the column is maintained at a preset temperature in a **thermostatically controlled oven**.
- **An injection port:** It can accept either a gas or a liquid.

For a **gas sample**, the injection should be as rapidly as possible by an appropriate **gas-tight syringe** through a rubber septum or by a **special gas-sampling valve**.

For a **liquid sample** (e.g., a blood sample), the port is **heated**; therefore, the injected liquids are **vaporized** and the volatile components can be analyzed.

- **A flow control:** It provides a steady stream of the carrier gas (and the sample) through the column (figure 7-84).

- **A detector:** It is present at the outlet of the column and is connected to the recorder to monitor the sequential appearance of the sample components. There are 3 types of detectors:

- 1- **The flame ionization detector:** (it is the typical detector): The gas mixture (the carrier gas and the sample) are mixed with hydrogen and air to produce a flame at the end of the column. The flame will ionize all the particles of the carrier gas, sample, hydrogen, and air. A polarized voltage is applied across the flame by two electrodes and a current is produced. The intensity of the current is directly proportional to the charged ionized particles in the flame e.g., **organic vapor**.

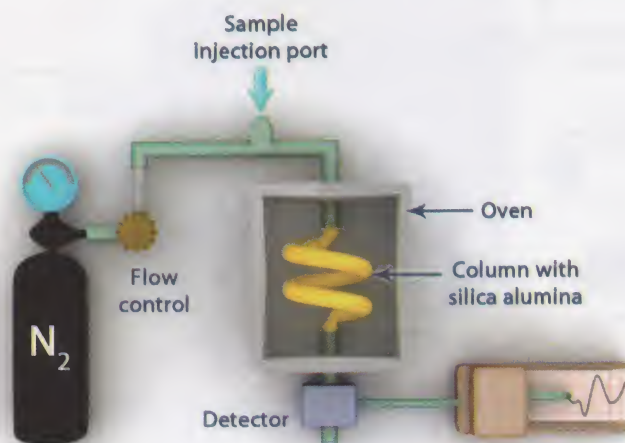


Figure 7-84: Gas chromatography

- 2- **The thermal conductivity detector (The katharometer):** It measures changes in thermal conductivity of the gas by the changes in the electrical resistance of a heated wire placed in the gas flow. It is the best one used for analysis of **inorganic gases** such as N_2O or O_2 .

- 3- **The electron capture detector:** A polarizing voltage is applied across an ionization chamber in which electrons, released from a radioactive cathode, constitute a flow of current to the anode. The sample captures these electrons and reduces the current flow. It is the best one used for analysis of **halogenated compounds** (figure 7-85).

- **A recorder:** It records the results of gas chromatography in the form of **peaks**. Each component of the sample passing out of the column (figure 7-86) has its specific peak, which appears at a certain period after the injection of the sample.

The retention time; is the time between the injection of a sample and its appearance at the detector. It is used to identify the components of the sample by comparing the peak of each component with the peaks of different pure previously known substances i.e., the peak of a certain component in the sample will match a peak of a previously known substance and, so identification of the component is achieved.

The peak heights or areas permit calculation of the quantity of each component.

Uses:

- Measurement of anesthetic agents, both for anesthetic concentrations and for trace levels in the operating theater atmosphere.
- Measurement of barbiturates, phenothiazines, benzodiazepines, steroids, and catecholamines after heating them and converting them into volatile compounds.

Advantages:

- It can identify and measure **very low concentrations** of substances as drugs even in a mixture of compounds.
- The **sample** can be either **gas or liquid**.

Disadvantages:

- It cannot allow the absolute identification of the unknown components of a sample. It is necessary to **have a preliminary knowledge of the types of substances present in the sample**. This allows injection of known quantities of different substances suspected to be in the sample to obtain their peaks and compare them with the peak of the component to be tested.
- It does **not allow continuous analysis**; therefore, it is rarely used intraoperatively. It is bulky and less convenient for use intraoperatively. It is only used inside laboratories.

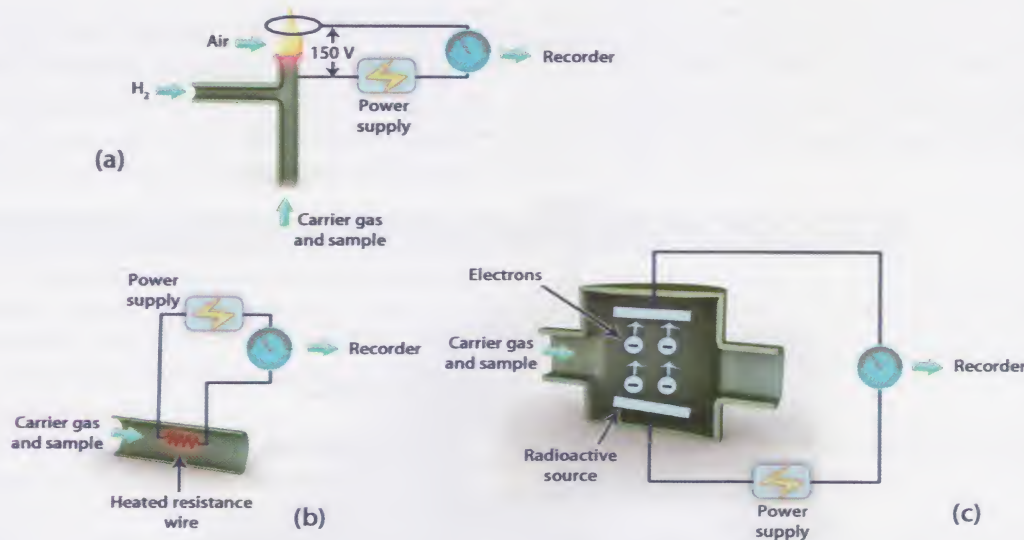


Figure 7-85: Flame ionization detector (a), thermal conductivity detector (b), and electron capture detector (c)

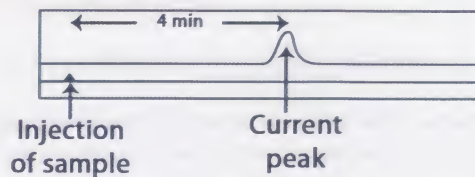


Figure 7-86: Gas chromatography recording trace

2- Mass Spectrometry:

It identifies compounds according to their **mass numbers**.

Idea:

- The gas sample is withdrawn from a side port in a breathing circuit elbow, into the device by a **vacuum pump** through a long tube of 1 mm width.
- The **molecules** of the gas sample are **ionized by an electron beam** passing from a hot cathode to an anode. The charged ions are then **accelerated** out of the ionizing chamber in a narrow beam **by means of acceleration and focusing plates**.
- The ionized molecules then **pass through a strong magnetic field**. The charged ions are deflected in an arc by the magnetic field. The amount of deflection depends on their mass. **The lighter ions are deflected most and follow a curved path with the smallest radius** while the heaviest ions are deflected least and follow a curved path with the greatest radius (figure 7-87). The spectrum of ion deflection forms the basis of analysis and separation of the components of the gas mixture.
- Only one of the ionized molecules passes through a **small slit** to be picked up by a **detector**. By varying the voltage on the acceleration and focusing plates, the position and speed of the beam may be altered and streams of ions of different masses can be detected.
- Another method of detection of specific molecules is called "**Quadrupole mass spectrometer**".

4 electrically charged rods are present instead of the magnetic field. The electrical potentials on the rods are varied so that the ions oscillate between them as they travel. The ions can be arranged, as only the ions of a specific mass are able to travel the length of the rods without being removed from the stream.

• **Many molecules fragment** during the process of ionization into smaller particles e.g., during detection of CO_2 (its mass number is 44), the mass spectrometer will detect **carbon monoxide** and O_2 (their mass numbers are 28 and 16 respectively) due to fragmentation of the molecules of CO_2 .

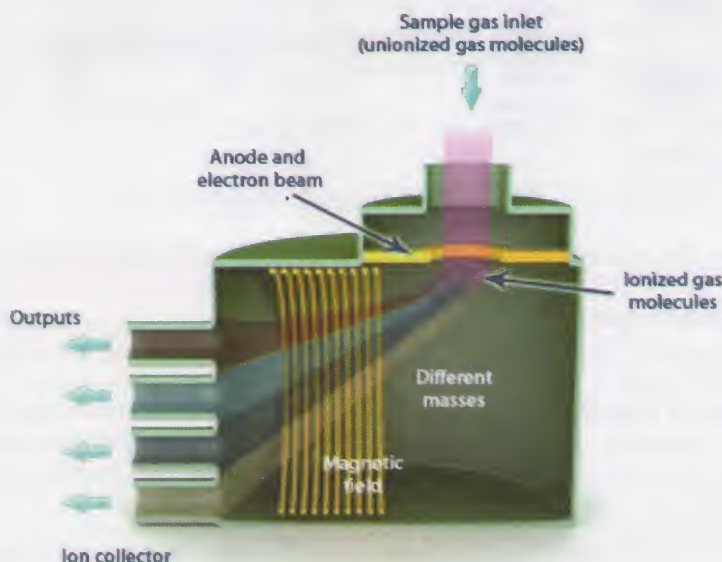


Figure 7-87: Mass spectrometer

• During analysis of a gas mixture, large numbers of ions are produced and some may have the same mass number, which may give a false result. Therefore, to measure a certain component of the gas mixture, one of its ionized fragments is chosen which has a specific mass number different from any other ions in the gas mixture e.g., both N_2O and CO_2 have the same mass number of 44. The nitrous oxide fragments on ionization give a smaller nitric oxide fragment with a mass number of 30 which can be identified and used to measure the concentration of nitrous oxide.

Uses:

It can be used to measure water vapor, O_2 , CO_2 , and other gases e.g., during breath analysis of expired air. Nowadays, because of cost considerations, it is used mainly as a research tool.

Disadvantages:

It is bulky and less convenient for use intraoperatively. It is only used inside laboratories.

3- Raman Spectroscopy or Spectrometry:

Idea:

When radiation falls on a molecule, the molecule may absorb the radiation as occurs with CO_2 and infrared absorption spectrophotometry. Other molecules may partially transfer the energy of the radiation to the molecule and this is called **the Raman Effect**.

When the energy is transferred from the radiation to the molecule, the wavelength of the radiation is decreased. The decrease in the wavelength is a characteristic of an individual type of molecule and is also proportional to the concentration of the measured gas.

An intense source of light, typically a **laser** (e.g., a helium-neon laser) is used to generate enough Raman radiation to achieve a measurable signal at a detector.

The radiations are detected by a photo-detector that converts the radiation to electrical signals.

Advantages:

- Accurate as mass spectrometers
- Faster response time.
- Self calibration.
- Increased durability.

4- Quartz Crystal Oscillators:

Idea:

When an electric potential is applied across a crystal of quartz, it slightly contracts; this is known as **the piezoelectric effect**. When a suitable alternating potential is applied to the quartz crystal, it oscillates at a specific resonant frequency. The crystal is covered by a thin coat. The resonant frequency of the crystal changes according to the type and concentration of the substances dissolved in the thin coat.

Therefore, when a volatile gas is applied, it dissolves in the thin coat and alters the resonant frequency of the crystal which can indicate the type and amount of the vapor gas. This oscillation produces an electrical signal proportional to the vapor concentration.

Uses:

- For measuring anesthetic vapor concentration e.g., in the closed circuit.
- For calibration of vaporizers.

5- Infrared Analyzer (Infrared Spectroscopy or Spectrometry):

Idea:

It uses the principles of **the infrared absorption spectrophotometry** (see before in the capnography).

There are two types:

- **Monochromatic infrared spectroscopy:** as an infrared beam of light with a wavelength of 3300 nm is absorbed by the gas sample. The halogenated agents absorb this light identically; therefore, it is used to identify the halogenated agent.
- **Polychromatic infrared spectroscopy:** uses an infrared wave between 7000-13000 nm. The absorption spectrum of inhaled anesthetic drugs is relatively different at this wavelength; therefore, this allows identifying the type of the gas and its concentration and can even measure the concentrations of two drugs simultaneously.

There are many variations which include:

- Acoustic sensing.
- Near-infrared optical sensing.
- Far-infrared optical sensing.

Because O₂ molecules do not absorb infrared light; therefore, they can not be measured by this method.

Uses:

- For calibration of vaporizers.

6- Refractometer (Interferometer)

Idea:

- Two light beams pass through the refractometer; one through a sample chamber and one through a reference chamber (figure 7-88).

If the two beams are added together while they are in the same phase, the amplitude increases giving rise to a **bright fringe**.

If the two beams are added together while they are out of phases, the amplitude decreases giving rise to a **dark fringe**; therefore; an array of light and dark fringes results.

- When the reference chamber is left unchanged and an unknown concentration of sample gas is added to the sample chamber, the velocity of the light passing through the sample chamber is reduced; therefore, the phases of the waves are altered when the two light beams are recombined. This leads to displacement of the fringe pattern, which can be observed through an eyepiece. The displacement of a selected fringe is directly proportional to the concentration of gas added to the sample chamber.

Uses:

- For calibration of vaporizers.

Advantages:

- Small portable refractometers are available.
- Very sensitive versions are available.

Disadvantages:

- It cannot be used to identify component gases in a mixture and so these component gases must be known in advance.

Methods 4, 5, and 6 can be used to check the calibration of vaporizers.

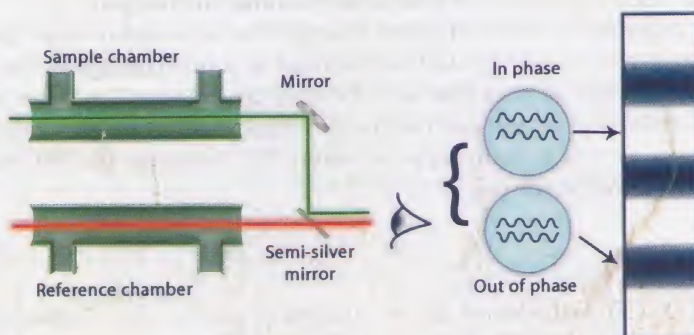


Figure 7-88: The refractometer

VIII- Pulmonary Function Tests

include:

- 1- Measurement of static lung volumes and capacities.
- 2- Measurement of dynamic lung volumes and capacities.
- 3- Measurement of flow volume loops.
- 4- Measurement of lung compliance.
- 5- Measurement of ventilation/perfusion relationship.
- 6- Measurement of diffusion through alveolo-capillary membrane.
- 7- Differential pulmonary function tests.

1- Measurement of Static Lung Volumes and Capacities

The normal values of all volumes differ according to the patient's sex, age, height (they are more related to the height than the weight of the patient).

They include **tidal volume**, **inspiratory reserve volume**, **inspiratory capacity**, **expiratory reserve volume**, **residual volume**, **functional residual capacity**, **vital capacity**, **closing volume**, **closing capacity**, and **thoracic gas volume**.

Definitions of these volumes and capacities are discussed in details in chapter "Anesthesia & Respiratory diseases".

Methods of Measurements:

Simple Bedside Tests:

They are inaccurate but simple and may be done without any sophisticated device. They include:

1- Schneider match test:

A candle is placed in front of the mouth of the patient 6 inches (50 cm) away. The patient is asked to blow air to extinguish the flame. Failure to extinguish the flame indicates that vital capacity is below 25% the normal i.e., there are gross cardio-pulmonary abnormalities.

2- De Bono whistle:

It is a transparent whistle with a ball inside that moves along a scale. The patient is asked to take a deep breath then to blow inside the whistle to move the ball. The degree of movement of the ball indicates the pulmonary function of the patient.

All lung volumes (except residual volume, functional residual capacity, closing capacity, and total lung capacity): may be measured by different ways e.g., **Benedict Roth spirometer**, **respiratory inductance plethysmography**, **Wright respirometer**, and **vitalograph**. For more details see gas volume measurement in chapter "Basic Physics for Anesthesia & Intensive Care".

Measurement of residual volume (RV), functional residual capacity (FRC), and total lung capacity (TLC): are measured by **Washout and Dilution Methods**:

1- Nitrogen Washout Method (Open-Circuit Method):

Idea:

The patient breathes air through a non-rebreathing valve:

- If the **FRC** is required, two additional valves are turned **at the end of a normal expiration** so that the inspired gas is abruptly changed to pure oxygen, whilst the expired gas is directed into an empty Douglas bag free from nitrogen (a large tight bag).
- If the **RV** is required, the previous step is done **after maximal expiration**.

- If the **TLC** is required, the previous step is done **after maximal inspiration**.

The patient continues to expire for several times through the non-return valve into the bag until the nitrogen has been washed out of the lungs and is measured by a **nitrogen meter** i.e., the concentration of nitrogen exhaled from the lung becomes less than 2% (this takes about 7 minutes in those with normal lungs) and the volume of the expired gas and its nitrogen concentration are measured.

Since the gas in the lungs initially contains approximately 80% nitrogen, the FRC must be 100/80 times the volume of nitrogen collected in the bag.

$$\begin{array}{rclclcl}
 V_1 & \times & C_1 & = & V_2 & \times & C_2 \\
 \text{Volume of gas in} & \times & \text{Concentration of N}_2 & = & \text{Volume of gas in} & \times & \text{Concentration of N}_2 \\
 \text{the lung e.g., FRC} & & \text{in air (in lungs)} & & \text{Douglas bag} & & \text{in Douglas bag} \\
 \\
 \text{FRC} & \times & 80/100 & = & \text{Amount of N}_2 \text{ in Douglas bag} & & \\
 \\
 \text{FRC} = & \frac{\text{Amount of N}_2 \text{ in Douglas bag}}{80/100} & & & & & \\
 \\
 \text{FRC} = & \frac{\text{Amount of N}_2 \text{ in Douglas bag} \times 100}{80} & & & & &
 \end{array}$$

In practice, a correction factor must be applied for:

- The volume of nitrogen eliminated into the lungs from the tissues during the washout period.
- The small quantity remaining in the alveoli at the end of the washout period.

2- Helium Dilution Method (Closed-Circuit Method):

Idea:

• A measured volume of an insoluble gas such as helium (i.e., not diffusible through the alveolo-capillary membranes) is added to a spirometer containing oxygen. The gases (helium and O₂) are mixed by recirculating around the closed circuit of the spirometer.

- **The volume of the spirometer circuit V₁ is derived from the volume of helium added and its final concentration.**

If the **FRC** is required, the spirometer is then connected to the patient **at the end of expiration**.

If the **RV** is required, the spirometer is connected to the patient **at the end of maximal expiration**.

If the **TLC** is required, the spirometer is connected to the patient **at the end of maximal inspiration**.

- The patient continues to re-breathe into the spirometer until the gases in the lung and spirometer are thoroughly mixed and equilibrium occurs between them.

$$V_1 \times C_1 = (V_1 + \text{FRC}) \times C_2$$

Where V₁ = volume of gas in the spirometer.

C₁ = the initial concentration of helium in spirometer before mixing and breathing.

V₂ = volume of patient's lung (e.g. FRC) and volume of spirometer i.e., FRC + V₁

C₂ = concentration of helium in both lung and spirometer i.e., after mixing and breathing.

Therefore, FRC can be calculated as follows:

$$V_1 \times C_1 = (V_1 + \text{FRC}) \times C_2$$

N.B.: In patients with **airway obstruction e.g., severe emphysema**, the dilution method will give **lower values** because the volume of the trapped gas will not equilibrate with the inert gas. Therefore, total body plethysmography is used instead.

Measurement of Closing Capacity (CC):

By **Single-Breath Nitrogen Test**

Idea:

The patient is allowed to take a deep breath with 100% oxygen and hold his breath for a few seconds, and then the patient **expires slowly**, where the volume of expired gas and nitrogen concentration in the expired gas are measured (by a nitrogen meter) and plotted on a curve (figure 7-89).

From the curve;

- **Phase I:** corresponds to the **dead space** where only O₂ is present without nitrogen.
- **Phase II:** corresponds to the transition zone i.e., **mixing** between the dead space and the alveolar gas.

- **Phase III:** corresponds to the **alveolar gas** where a plateau occurs.
- **Phase IV:** corresponds to the **closing volume**. The concentration of nitrogen increases until it stops suddenly. This occurs because at this phase of the end of expiration, the gas exhaled from the smaller airways decreases while that from the larger airways continues to be exhaled where the larger airways contain higher concentration of the nitrogen i.e., it denotes the lung volume from the beginning of airway closure to the end of maximal expiration.

N.B.: Other gases can be used to measure the closing volume and capacity such as xenon¹³³ or argon.

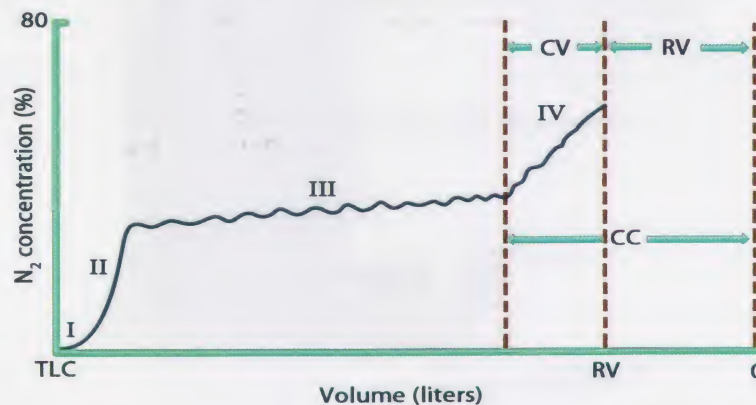


Figure 7-89: Single-breath nitrogen test

Measurement of Thoracic Gas Volume:

By **Total Body Plethysmography**

It is used to measure airflow rates, changes in lung volumes, thoracic gas volume, and airway resistance. It is mainly performed for research works.

Idea:

- The patient sits in a sealed box and breathes through a tube connected to a pneumotachograph. The sealed box is represented by a **constant volume plethysmograph** where the change in the lung volume creates a change in the pressure in the box, which is sensed by a sensitive pressure transducer (figure 7-90).
- To measure **thoracic gas volume (V_1)**, the patient makes inspiratory and expiratory efforts against a **closed shutter** (i.e., a panting procedure) whilst the change in the **mouth pressure (ΔP)** and the change in the **box volume (ΔV)** are recorded. During these panting efforts, the gas in the lungs is alternately compressed and expanded by the action of the chest muscles.
- Since there is no flow of gas through the airways, **changes in mouth pressure** accurately **reflect** the changes in the **pressure of the intra-thoracic gas** in response to the changes in chest wall volume.
- By applying Boyle's law ($PV = k$), the following equation can be derived:

$$P_1 V_1 = P_2 V_2$$

Where: P_1 is the barometric pressure minus water vapor pressure.

V_1 is the thoracic gas volume.

P_2 is the sum of P_1 and ΔP

V_2 is the subtraction of ΔV from V_1 .

Therefore, the equation can be written as follows:

$$P_1 V_1 = (P_1 + \Delta P)(V_1 - \Delta V)$$

N.B.: Body plethysmography also can measure **airway resistance (R)** as the patient breathes through the pneumotachograph. The following equation is used:

$$R = \frac{\Delta P}{\Delta V} \times \frac{\Delta V}{v}$$

Where: R is the airway resistance.

v is the instantaneous flow rate recorded by the pneumotachograph.

Advantages:

- The airway resistance recorded is a reliable measure because it is unaffected by the tissue resistance.
- It obviates the need to swallow an esophageal balloon for measurement of esophageal pressure which is used in measurement of airway resistance.

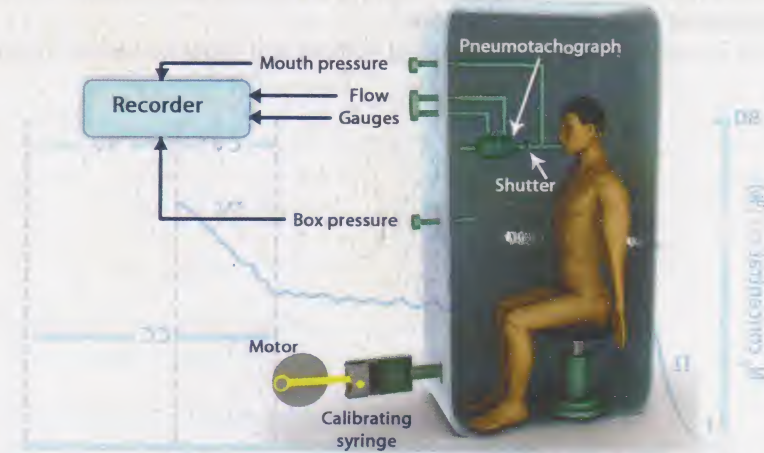


Figure 7-90: Total body plethysmograph

2- Measurement of Dynamic Lung Volumes and Capacities

Includes:

1- Maximum Breathing CapacityDefinition:

It is the maximal volume of air that can be inspired with maximal breathing effort i.e., the fastest and the deepest breaths per minute.

Normal values are for males = 80-160 L/min.

for females = 60-120 L/min.

It is a better index for respiration than the vital capacities.

N.B.: Breathing Reserve:

It is the difference between the maximal breathing capacity and the resting minute volume i.e.,

$$\begin{aligned}\text{Breathing reserve} &= \text{maximal breathing capacity} - \text{minute volume} \\ &= 100 - 6 = 94\end{aligned}$$

The normal value is expressed as a percentage, as it is compared to the maximum breathing capacity i.e., 94%. If it decreases to 60-70%, dyspnea occurs (this is called the **dyspnic index**).

Method of Measurement:

By the **Wright respirometer**

The patient is allowed to breathe forcibly for 15 seconds then the result is multiplied by 4.

2- Timed Vital Capacity (Forced Expiratory Volume, FEV)Definition:

After the patient does maximal inspiration, it is the amount of air that can be expired after forced expiration in the first (FEV₁), second (FEV₂) and third (FEV₃) seconds of respiration.

It is usually compared with the forced vital capacity (FVC) i.e., **FEV₁/FVC ratio**. It indicates the degree of airway obstruction.

Normal values are $\text{FEV}_1/\text{FVC} = 83\%$

$\text{FEV}_2/\text{FVC} = 94\%$

$\text{FEV}_3/\text{FVC} = 97\%$

Method of Measurement:

It is measured by the **vitalograph**.

3- Peak Expiratory Flow Rate (PEFR)Definition:

It is the maximum velocity of airflow that can be produced by the patient during forced expiration.

Normal values are for males = 500-700 L/min.

for females = 300-500 L/min.

Method of measurement

It is recorded on a graph,

before, the dead space is measured with a peak spirometer.

The flow-volume loop is compared to a nomogram (special tables containing the average normal values according to height) to give the values as a percentage to the normal value.

3- Measurement of Flow Volume Loops**Definition:**

They provide a graphic analysis of flow at various lung volumes.

Technique:

- Both flow and volume are plotted simultaneously on an X-Y recorder as subjects fully inspire to total lung capacity (TLC) and then perform a forced vital capacity (FVC) maneuver. This is immediately followed by a maximal inhalation as fast as possible back to TLC (figure 7-91).

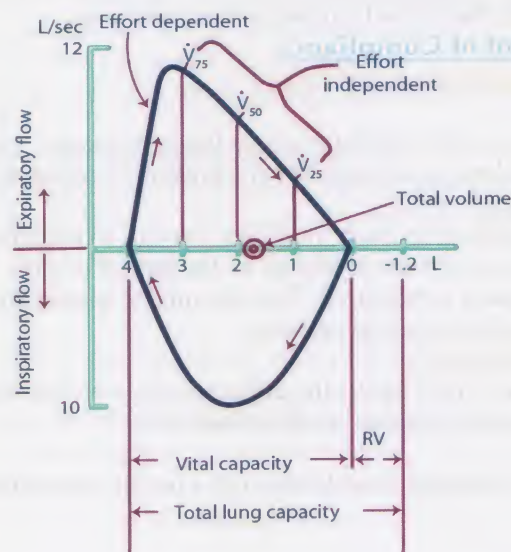


Figure 7-91: Flow-volume loops

- The entire inspiratory portion of the loop and the expiratory curve near TLC are highly effort dependent, whereas the expiratory flow at 75% to 25% of VC is effort independent.
- V_{75} , V_{50} and V_{25} represent flow at 75%, 50% and 25% of the vital capacity.
- This loop can assess many of the functions of the lung and can be used to diagnose and assess many respiratory diseases.

4- Measurement of Lung Compliance

Compliance (C): It is sometimes called distendability or stretchability.

It is volume change per unit of distending pressure (mL/cm H₂O). It is due to tissue elasticity and surface tension.

$$C = \frac{\Delta \text{Volume}}{\Delta \text{Pressure}}$$

$$C_{\text{lung}} = \frac{\text{Change in lung volume}}{\text{Change in trans-pulmonary pressure}} = 200 \text{ mL/cmH}_2\text{O}$$

$$C_{\text{chest}} = \frac{\text{Change in chest volume}}{\text{Change in trans-thoracic pressure}} = 200 \text{ mL/cmH}_2\text{O}$$

Total respiratory system compliance = 100 mL/cm H₂O

$$\frac{1}{C_{\text{total}}} = \frac{1}{C_{\text{chest}}} + \frac{1}{C_{\text{lung}}}$$

Pressure-Volume Curve (Compliance Curve)

It is discussed in details in chapter of "Anesthesia & Respiratory diseases".

Compliance can be measured either during static or dynamic states.

Static Compliance:

It is the ratio of tidal volume to the elastic pressure (i.e., plateau pressure). It is measured during **breath holding**. It is measured **intermittently** by changing the volumes entering or leaving the lungs i.e., it is measured at zero air flow.

The only affecting factor is the regional elasticity of the lung. Airway resistance has no effect.

Dynamic Compliance:

It is measured **during respiration by continuous** recording of the pressures and volumes of the lungs. It is drawn as loops (the **pressure volume loops**).

It is affected by the airway resistance.

N.B.: In emphysema, static compliance increases due to breakdown of the alveolar septa while the dynamic compliance decreases due to the increased airway resistance

Methods of Measurement of Compliance:

a) Measurement of Total Compliance of the Thorax:

1- Tank Ventilator:

A conscious patient is put on a tank ventilator where the intra-thoracic pressure can be measured. The volume of air inspired at each level of sub-atmospheric pressure is measured.

2- Positive Pressure Ventilator:

An anesthetized patient is put on an ordinary ventilator through an endotracheal tube. A muscle relaxant is given to abolish any airway resistance produced by the patient's effort. The tube is then temporarily occluded and the airway pressure is measured. Then the tube is opened and the volume of expired air is measured. Therefore, the compliance can be assessed.

b) Measurement of Lung Compliance:

The trans-pulmonary pressure (which equals the difference between the airway pressure and the pleural pressure) is measured. The pleural pressure can be measured by:

1- A Direct Method:

The pleural pressure can be measured directly through a needle inserted in the pleural cavity which is connected to a manometer.

2- An Indirect Method:

By measuring the esophageal pressure which equals the pleural pressure. The esophageal pressure is measured by an esophageal balloon inserted through the esophagus.

c) Measurement of Chest Wall Compliance:

Chest wall compliance = total compliance - lung compliance.

5- Measurement of Ventilation/Perfusion Relationship

It includes - measurement of dead space,

- measurement of venous admixture and shunt,

and - assessment of ventilation and perfusion.

A) Measurement of Dead Space:

Definitions of anatomical, alveolar, and physiological dead spaces are discussed in chapter of "Anesthesia & Respiratory diseases".

Methods of Measurement:

a) Measurement of the Anatomical Dead Space:

By **single-breath nitrogen test**: See above.

b) Measurement of Physiological Dead Space:

1- Bohr's Equation:

Dead space = tidal volume - alveolar air

The CO₂ content in the dead space is approximately zero and the CO₂ in the expired air comes only from the alveolar gas. Therefore,

The expired air volume x its CO₂ concentration = alveolar air volume x its CO₂ concentration

So, the alveolar air volume = $\frac{\text{The expired air volume} \times \text{its CO}_2 \text{ concentration}}{\text{Its CO}_2 \text{ concentration}}$

$$= \frac{500 \times 0.04}{0.056} = 357 \text{ mL}$$

Therefore, the dead space = $500 - 357 = 143 \text{ mL}$

2- Enghoff Modification of Bohr's Equation (Modified Bohr Equation):

Dead space (V_{Dn}) = tidal volume $\times \frac{\text{CO}_2 \text{ concentration in the alveolar air} \times \text{CO}_2 \text{ concentration in expired air}}{\text{CO}_2 \text{ concentration in alveolar air}}$

As CO_2 concentration in the alveolar gas = CO_2 concentration in the arterial blood, the equation can be written as follow:

$$V_d = V_t \times \frac{P_a\text{CO}_2 - P_e\text{CO}_2}{P_a\text{CO}_2} \quad \text{therefore,} \quad V_d/V_t \text{ ratio} = \frac{P_a\text{CO}_2 - P_e\text{CO}_2}{P_a\text{CO}_2}$$

Where: $P_a\text{CO}_2$ = CO_2 tension in the arterial blood. It is obtained by an arterial sample.

$P_e\text{CO}_2$ = CO_2 tension in the expired air. It is obtained by collecting mixed expired gas in a Douglas bag and subjecting this to analysis, or by using a capnography.

V_t = the tidal volume. It is obtained by any method that measures the volume.

For example, if $P_a\text{CO}_2 = 40 \text{ mm Hg}$ and $P_e\text{CO}_2 = 20 \text{ mm Hg}$, then $V_d/V_t = \frac{40 - 20}{40} = 0.5$

B) Measurement of Venous Admixture and Shunt

Definition of shunt and venous admixture is discussed in chapter "Anesthesia & Respiratory diseases". The venous admixture in normal individuals (physiologic shunt) is typically less than 5%.

$$\text{Virtual shunt fraction: } \frac{Q \cdot s}{Q \cdot t} = \frac{C\bar{c}\text{O}_2 - C_a\text{O}_2}{C\bar{c}\text{O}_2 - C\bar{v}\text{O}_2}$$

$C\bar{c}\text{O}_2$ = O_2 content of end pulmonary capillary blood in mL/100 mL blood. It is obtained by a pulmonary artery catheter during wedging.

$C_a\text{O}_2$ = O_2 content of arterial blood in mL/100 mL blood. It is obtained from an arterial catheter.

$C\bar{v}\text{O}_2$ = O_2 content of mixed venous blood in mL/100 mL blood. It is obtained by a pulmonary artery catheter slowly without wedging.

$Q \cdot s$ = Venous admixture.

$Q \cdot t$ = Total cardiac output.

C) Assessment of Ventilation and Perfusion

By **Radioactive Isotopes**

1- Intravenous injection of xenon¹³³ can detect the areas of the lung that are perfused.

2- Inhalation of xenon¹³³ can detect the areas of the lung that are ventilated.

6- Measurement of Diffusion through Alveolo-Capillary Membrane

Because end-pulmonary capillary O_2 tension ($P\bar{c}\text{O}_2$) cannot be measured accurately, measurement of carbon monoxide diffusion capacity instead is used to assess gas transfer across the alveolar-capillary membrane.

Because carbon monoxide (CO) has a very high affinity for Hb, end-pulmonary capillary CO tension ($P\bar{c}\text{CO}$) can be considered zero. Therefore,

$$D_L\text{CO} = \frac{\text{Carbon monoxide uptake}}{P_{\text{ACO}}}$$

Where; $D_L\text{CO}$ = diffusion capacity of carbon monoxide

P_{ACO} = Carbon monoxide tension in the alveolar gas.

Decreased $D_L\text{CO}$ represents a decrease in gas transfer across the alveolar-capillary membrane e.g., due to:

- Abnormal ventilation/perfusion ratio.
- Extensive destruction of alveolar-capillary membrane.
- Very short capillary transit times i.e., severe tachycardia.

7- Differential Pulmonary Function Tests

Pulmonary function tests are done for each lung separately by using a double lumen tube while the patient is anesthetized e.g., radioactive xenon¹³³ inhalation can be done separately for each lung to assess lung perfusion.

The results of pulmonary function tests differ from patient to another according to the patient's height, weight, and sex; therefore, although the actual values done by the patient are obtained, the **percentage of the predicted**, which is the comparison of the patient's results to the normal values is obtained.

If they are **75-100% of the predicted**, they are considered **normal values**.

If they are **50-75% of the predicted**, they reflect **mild to moderate affection**.

If they are **less than 50% of the predicted**, they reflect **severe affection** and so postoperative ventilation is usually needed.

N.B.: Arterial blood gas analysis can be used to assess lung function.

Differentiation between obstructive and restrictive lung diseases is discussed in details in chapter "Anesthesia & Respiratory diseases".

PART 3: MONITORING OF THE NERVOUS SYSTEM

- It includes:
- 1- Clinical monitoring.
 - 2- Electroencephalography (EEG).
 - 3- Evoked potentials.
 - 4- Cranial nerve monitoring.
 - 5- Cerebral blood flow measurement.
 - 6- Monitoring of cerebral oxygenation.
 - 7- Monitoring of the intracranial pressure.
 - 8- Multi-modal neuro-monitors.
 - 9- Monitoring of depth of anesthesia.
 - 10- Neuromuscular monitoring.

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I- Clinical Monitoring

A- Glasgow Coma Scale (GCS):

It is used pre-, or postoperatively.

Category	Score
1- Eye opening:	
• Spontaneous	4
• To verbal command	3
• To pain	2
• No response	1
2- Best motor response:	
• To verbal command: Obeys	6
• To pain - Localizes pain	5
- Flexion withdrawal	4
- Abnormal flexion (Decorticate rigidity)	3
- Extensor response (Decerebrate rigidity)	2
- No response	1
3- Best verbal response:	
• Oriented and converse	5
• Disoriented and converse (confused)	4
• Inappropriate words	3
• Incomprehensible sounds	2
• No response	1

The highest score is 15 and the lowest score is 3

- Mild head injury: GCS 13-15.
- Moderate head injury: GCS 9-12.
- Severe head injury: GCS 3-8 with 35% mortality.

B- Assessment of the Depth of General Anesthesia:

By the clinical picture (see later).

C- Awake Test or Wake Up Test:

The patient is either anesthetized by regional techniques or allowed to wake up during surgery and then asked to respond to a verbal command.

Indications:

- 1- Cerebral surgery for resection of a seizure focus.
- 2- Carotid endarterectomy: The test is done before, 1, and 2 minutes after clamping of the carotid artery to assess the contra-lateral motor function.
- 3- Surgical correction for scoliosis: It is done to assess the anterior spinal cord motor pathways.

Values:

- 1- Simple and inexpensive.
- 2- It can test areas of the brain that are not assessed by electro-physiological methods e.g., speech.
- 3- It is a **reliable and sensitive** test. It is affected when cerebral blood flow (CBF) is reduced to 25 cc/min/100g brain tissues. It is more sensitive than electroencephalography (EEG) and somatosensory evoked potentials (SSEPs) because they are affected only when the CBF is reduced to 15-20 cc/min /100 g brain tissues.

II- Electroencephalography (EEG)

A) Unprocessed Raw EEG:

Idea:

It records the intrinsic electric activity of cerebral neurons, mainly the pyramidal neurons in laminae I, II and V within the cerebral cortex by summation of the excitatory and inhibitory postsynaptic potentials in the neuron pathways causing recorded waveforms by:

- A full 16 lead, 8 channel EEG.
- For intraoperative monitoring, 2-4 leads can be used only.

Electrodes are arranged by the international 10-20 system (called **montage**). Sterile standard electrodes can be put directly in the surgical field (figure 7-92).

The recorded waveforms are then filtered, amplified and displayed by an oscilloscope or pen recorder.

Disadvantages:

- Difficult to be interpreted requiring specially trained personnel.
- Difficult in obtaining a meaningful recording in the electrically noisy environment of the operation room.
- The bulk of the equipment required.

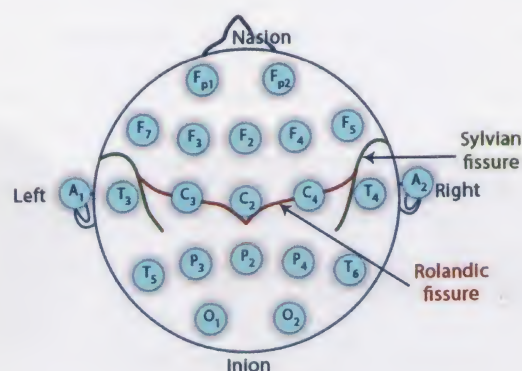


Figure 7-92: International 10-20 system

EEG Waveforms: (figure 7-93)

- In relaxed adults with closed eyes, α rhythm predominates.
- With eye opening i.e., any sensory stimulation "excitation or arousal", fast irregular low voltage activity with no dominant rhythm called **α block or de-synchronization** predominates.
- In children, θ rhythm predominates.

- In non-rapid eye movement (NREM, deep) sleep, large irregular δ waves interrupted by α - like activity predominate.
- In rapid eye movement (REM, paradoxical) sleep, low voltage irregular rapid waves predominate.

Rhythm	Frequency (Hz)	Amplitude (μ v)	Figure 7-93
Beta (β)	14-30 (fastest)	< 20	
Alpha (α)	8-13	20-50	
Theta (θ)	4-7	20-50	
Delta (δ)	< 4 (slowest)	> 50	

B) Processed EEG:

Various methods of signal processing and computer-assisted data analysis have been developed which compress the data and make interpretation easier and more acceptable. These include:

1- Cerebral Function Monitor (CFM): introduced in 1969

It compresses all frequencies and amplitude information in the EEG into a single value. It uses 2 parietal electrodes and one midline electrode anterior to the vortex which records frequencies within 2-15 Hz only (to reduce artifacts and interference). These signals are amplified, integrated and compressed to produce a slow-running chart recording as a line, the height of which (above the baseline) indicates the total power (figure 7-94).

Value: Besides the values of EEG "see later".

1- It permits continuous monitoring of electrical activity.

2- It can detect changes in the **depth of total intravenous anesthesia**, but it is **unreliable when volatile agents are used**.

Disadvantages:

- The record is neither one of frequency nor of amplitude, but a mixture of the two, so it requires supplementation at regular intervals by a full EEG due to loss of information by processing.
- It does not detect focal activity, but assesses the whole cerebral function.

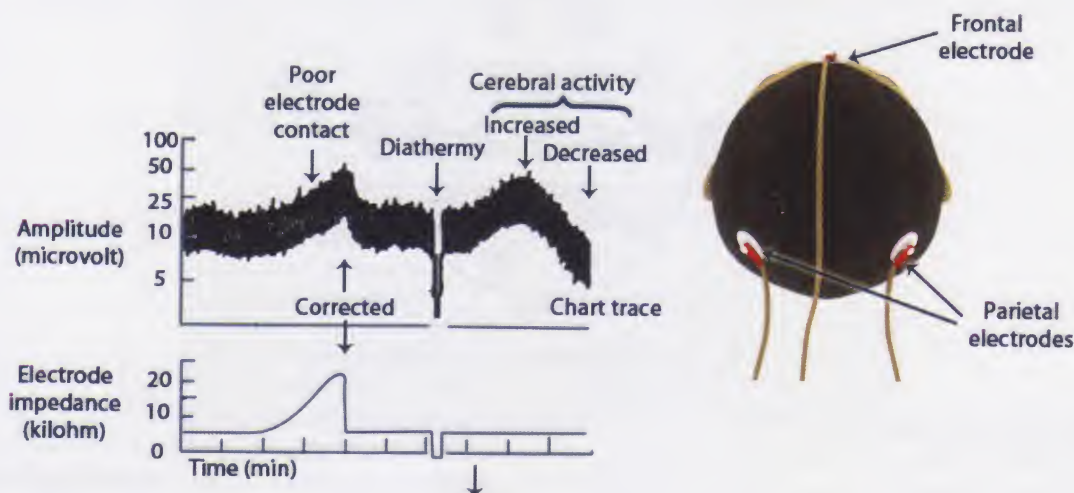


Figure 7-94: Cerebral function monitor

2- Cerebral Function Analyzing Monitor (CFAM):

Introduced in 1984

Idea:

It uses 3 or 4 electrodes that are positioned over the vertex. These positions avoid the frontal and temporal regions where there is more possibility of picking up slow waves due to eye movement or fast components from the scalp or facial musculature.

It provides analysis of both the amplitude and frequency. It displays a percentage of each band (α , β , θ , δ) and the mean, 10th and 90th percentiles of the overall EEG amplitude (figure 7-95). It also detects muscle activity by measuring spontaneous scalp electromyogram (EMG) to detect patient activity, and electrode impedance to detect interference.

Value:

- It can detect the **depth of anesthesia and sedation**, as initial stimulation followed by depression (see later).
- It can detect the increased cerebral activity of **status epilepticus** and the effectiveness of anti-convulsant therapy.

Disadvantages:

It is only a general indicator of metabolic activity and this may be depressed by a variety of causes such as brain edema, hypoxia, trauma, hypotension, or metabolic encephalopathy.

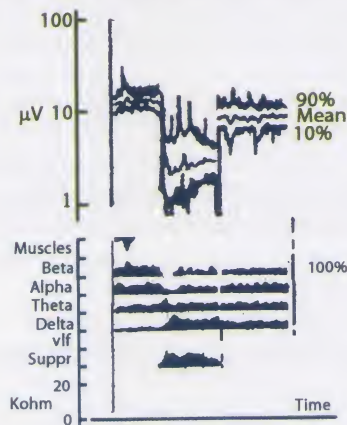


Figure 7-95: Cerebral function analyzing monitor

3- Power Spectrum Analysis:

Idea:

It retains all information from the original EEG, changing the complex waveforms of an unprocessed raw EEG into a number of standard waves for easy comparison by using Fourier analysis or transformation (figure 7-96) which is displayed graphically. It studies the EEG at short time intervals, known as epochs (2-16 s). 8 seconds are usually chosen.

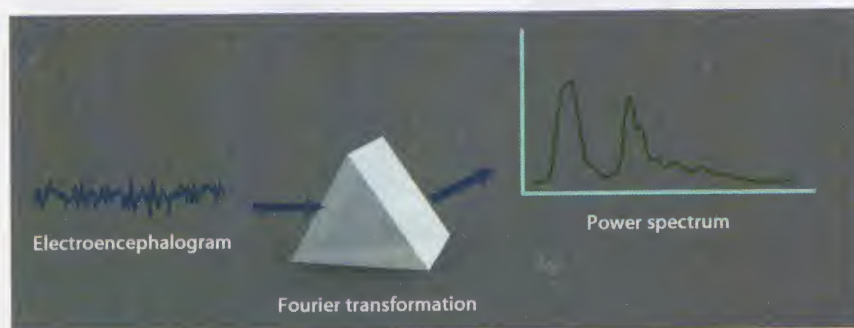


Figure 7-96: Fourier transformation of the raw EEG into a power spectrum

Advantages:

- 1- All information is retained and small changes may be readily identified.
- 2- Each frequency band may be studied separately.
- 3- It can detect differences between the two hemispheres.

- 4- It can monitor changes **during cerebral sedation and anesthetic techniques.**
- 5- It can detect ischemic changes better than the CFM and CFAM.

Disadvantages:

It discards any information concerning the phase relationship of the different waves.

- The power spectrum is displayed for each epoch graphically either as:

a- A Compressed Spectral Array (CSA):

Idea:

CSA shows processed EEG as a series of peaks and troughs, with time displayed along the vertical axis and frequency along the horizontal axis. The spectra for the previous epochs are shown above and behind the more recent ones i.e., the most recent data is at the bottom of the display.

The range of low to high frequencies is displayed from left to right. The relative power at any given frequency is shown by the height of the peak. It provides a pseudo-three-dimensional display of frequency against power distribution over time. High amplitude activity obscures subsequent lower-amplitude activity at the same frequency (figure 7-97).

Several attempts were done to extract single numbers from the CSA to **simplify the interpretation** such as:

- **Spectral edge frequency:**

It is the EEG frequency below which 95 % of EEG power is present i.e., it provides a measure of the upper edge of the power spectrum. It can **indicate the depth of anesthesia** as a progressive reduction in this value has been demonstrated with increasing concentrations of anesthetic agents but it is an **unreliable** technique because during the transition from deep to light levels of anesthesia, the relationship between spectral edge and drug concentration is poor.

- **Median frequency:**

It is the EEG frequency below or above which 50% of EEG power is present i.e., it represents the midpoint of the power distribution in the CSA. It is **more accurate** than the spectral edge frequency as an indicator for the depth of anesthesia because it provides a better relationship with the drug concentrations in both the induction and recovery phases of anesthesia. Different types of anesthetic agents give various patterns of CSA.

- **Peak power frequency:**

It is the EEG frequency at which the highest power (100%) is present.

b- Density Spectral Array (DSA):

Idea:

- It represents the amount of activity in epochs at each frequency, by a line running across a paper from low to high frequencies. So, it produces a grey-scale display.
- The greater the activity at any frequency is, the thicker the line will be (figure 7-98).

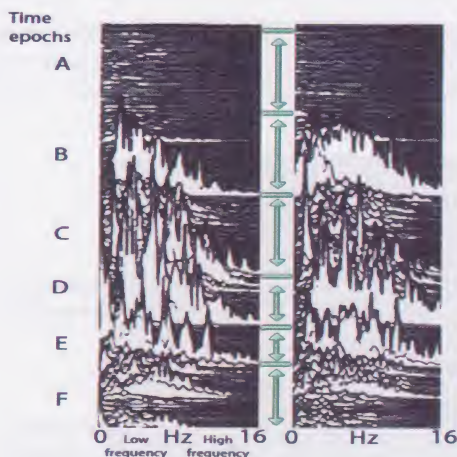


Figure 7-97: Compressed spectral array (right and left hemisphere)



Figure 7-98: Density spectral array (right and left hemisphere)

The Currently Available Processed EEG Monitoring Technologies:

For assessing the depth of anesthesia.

1- Bi-Spectral Analysis and Bi-Spectral Index (BIS):

Idea:

- It is the most **recent method** of processing EEG.
- A portion of the cortical EEG reflects changes attributable to harmonic and phase relationships between **cortical and subcortical** neural generators. These relationships are altered during hypnosis, producing characteristic pattern in the EEG.
- Bispectral analysis is based on:
 - Analysis of the **relationship between the phase and the power** for each wave of the EEG. In contrast, in the compressed spectral array, any information concerning the phase relationship of the different waves is discarded.
 - Using a mathematical calculation to **quantify the relationship between frequency triplets** present in EEG. Each wave has a **phase, power, and frequency**. Each two frequencies have **frequency triplets**, which are the two frequencies f_1 and f_2 and the sum of those frequencies $f_1 + f_2$.
 - Calculating a measure of **the phase relationship between the frequency triplets** which is known as the **bicoherence**. The bicoherence is a value between 0 and 1:
 - If the phase relationships between the frequencies in a triplet tend to be random, the bicoherence approaches 0.
 - If the phase differences between the frequencies tend to be fixed, the bicoherence approaches 1.

In case of **deep anesthesia**, the phase difference between the frequencies tends to be fixed and the bicoherence **increases and approaches 1**.

Therefore, bispectral analysis is a sophisticated signal processing methodology that assesses relationship among signal components and captures synchronization within signals like the EEG. This can indicate hypnosis.

Bi-Spectral Index (BIS):

It is the first commercially available system that algorithmically calculates the patient's EEG activity, bicoherence, and burst suppression and converts them to a single number (figure 7-99). It produces a **BIS scale** from 0 to 100.

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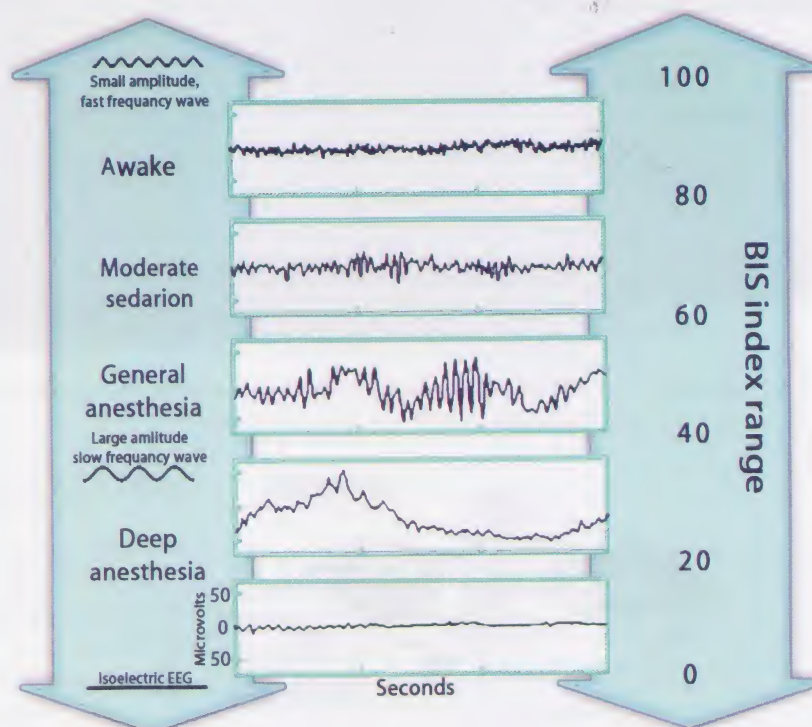


Figure 7-99: BIS scale

Where	95-100	= Fully awake.
	> 90	= Intact reflexes (i.e., patient can be extubated).
	70-85	= Light to moderate sedation.
	60-70	= Deep sedation.
	40-60	= Adequate depth of anesthesia
	< 40	= Deep anesthesia.
	0	= Isoelectric line of EEG.

It is **more reliable** than other types of processed EEG. It is a valid predictor of hypnosis and possibility of intraoperative awareness. It is currently accepted that induction and maintenance of anesthesia are associated with a decrease in BIS value, and that increasing concentrations of either volatile or intravenous anesthetics further decreases the BIS value. Therefore, it is a valid predictor of the depth of anesthesia.

Figures 7-100, 7-101, and 7-102 shows BIS electrodes, graphs, and a portable model.



Figure 7-100: Correct position of BIS electrodes on a child (left) and an adult (right); BIS electrodes are also shown.

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Figure 7-101: BIS monitor (left) and BIS response (right) with a skin incision (the patient is inadequately anesthetized as there is a rise of the scale).



Figure 7-102: The BIS module and compact portable BISx Power Link for software and signal processing.

Disadvantages and Limitations of BIS Index:

- 1- The BIS is **only a measure of the patient's level of sedation and hypnotic state rather than true global depth of anesthesia**. It does not predict patient movement or hemodynamic responses to noxious stimulation.
- 2- It **will not predict the exact moment when consciousness will return** because it is not a measure of global anesthesia depth and movement is primarily a spinal cord reflex.
- 3- Sedation produced by both **ketamine and N₂O do not produce the expected decrease in BIS**.
- 4- BIS is affected by:
 - Events as **cerebral ischemia or hypoperfusion**.
 - Drugs as **muscle relaxants and ephedrine**.
 - Conditions as **hypothermia and elderly** with low amplitude EEG.
 - Diseases affecting the brain as **hepatic failure**.

All the above conditions cause artifacts.

5- The BIS cannot be used in infants and children because the EEG is different than that of the mature brain of adult

6- Readings are affected in elderly patients with low amplitude EEG.

2- The Patient State Index (PSI):**Idea:**

- It is a processed parameter of a 4-channel EEG. The algorithm of PSI relies on 4-channel EEG providing information on power, frequency, and phase from anterior-posterior relationships of the brain as well as coherence between bilateral brain regions.
- Its new version is called the **"SEDLine EEG system"** (figure 7-103) with advanced artifact rejection techniques to further reduce the sensitivity to sources of electrical interference, in particular electrocautery. This new monitor can store up to 50 hours of raw and processed data. The addition of a dual, color density spectral array (DSA) provides the clinician with a concise spectral time history of EEG behavior permitting rapid assessment of frontal bilateral brain function.

Clinical Importance:

- PSI (and BIS) follows functional cerebral perfusion during periods of hypotension and resuscitation, and assesses as well as the level of hypnosis and/or depth of anesthesia for intra-operative and intensive care use to monitor patient sedation and drug effect.



Figure 7-103: SEDLine EEG system

3- Narcotrend Monitor**Idea:**

- The Narcotrend algorithm is based on pattern recognition of the raw EEG and classifies the EEG traces into different stages from A (awake) to F (increasing burst suppression down to electrical silence). In comparison with BSI, "100-85" BIS is equivalent to Narcotrend level of "A" or "B" i.e., fully awake status. "65-40" BIS is equivalent to Narcotrend level of "D" or "E" i.e., general anesthesia.

The newest Narcotrend software version includes a dimensionless Narcotrend index from 100 (awake) to 0 (electrical silence).

- Narcotrend monitor provides a vast amount of information; the actual Narcotrend stage and index, the trend (cerebrogram), the raw EEG signal and a power spectrum and several derived EEG parameters (figure 7-104).

Disadvantages

It is more accurate in assessing the depth of anesthesia of propofol-based anesthesia than other agents such as desflurane-remifentanyl based anesthesia.



Figure 7-104: Narcotrend monitor

4- Entropy:

Idea:

- Entropy is defined as the description of the irregularity, complexity, or unpredictability characteristics of a signal. Entropy can be explained in the following example of description of a state of a gaseous or fluid system. In a highly ordered system such as a crystal, every molecule has a preset place i.e., there are fewer possibilities of motion than in a disordered system such as fluid for distribution of molecules. During transition from a crystal to a fluid state (melting), entropy increases.

- Applying the concept of entropy to depth of anesthesia monitoring, it is suggested that during the awake state brain activity is more complex and produces more irregularity and complexity in the EEG signals. In contrast, if a person falls asleep or is anesthetized, brain function becomes more orderly and regular where entropy becomes less and decreases with increasing the depth of anesthesia.

- A 1-channel raw EEG is collected from the fronto-temporal region of the patient's head with self-adhesive Entropy sensor consisting of three electrodes. The signal is amplified, digitized, and processed.

- Entropy consists of two values; **state Entropy** (reflecting the cortical state of the patient i.e., EEG and indicating a **direct measure of the depth of anesthesia**) and **response Entropy** (reflecting the electromyographic component originating from **facial muscle activity** i.e., EMG and also indicating an **indirect measure of the depth of anesthesia** besides the **facial muscle activity**). Entropy module claims to separate out both EEG and EMG.

Actually both state Entropy and response Entropy decrease with the depth of anesthesia. By normalizing these two entropy parameters, response entropy becomes equal to state entropy when the EMG power is equal to zero, as the difference between response entropy and state entropy might serve as an indicator for EMG activation of facial muscles.

- Entropy is displayed as:

- state entropy: values are between 0 (totally suppressed EEG activity) to 100 (awake patient).
- response entropy values are between 0 (totally suppressed EEG activity) to 91 (awake patient)

The response entropy value is always higher or equal to the state entropy values. When no EMG activity is present, state entropy and response entropy show the same number.

Recommended range for adequate anesthesia for both parameters is from 40 to 60 and when state entropy increases above 60, the doses of anesthetics should be adjusted.

5- The SNAP Monitor:

- The SNAP monitor is a device intended for monitoring the effects of anesthetics. It consists of an EEG module included in a handheld computer. The snap algorithm is featured by its use of ultra-high EEG frequencies (80 Hz-420 Hz) additionally to the conventional low EEG frequencies (0 Hz-20 Hz). High-frequency EEG signals (around 200 Hz) seem to be involved in the regulation of the gamma band activity which, in turn, participates in the formation of consciousness. Therefore, its analysis allows the capture of the full range of the brain's electrical activity through the different stages of anesthesia.

- The signals are displayed as an SNAP index, which is a dimensionless numerical value ranging from: 100 (fully active brain state) to 0 (fully suppressed EEG activity).

- Since ultra-high frequency signals can be analyzed over shorter periods of time than low-frequency signals, the SNAP algorithm may be in theory **more responsive during the critical phases of induction and emergence**, allowing a closer analysis of the dynamic responses of the brain during the different stages of anesthesia and providing a **better-quality measure compared to similar devices**.

Factors Affecting EEG:

A- Anesthetic Agents:

There are characteristic changes in EEG occurring with deepening of anesthesia:

- **Light** anesthesia: EEG activation i.e., EEG shifts towards high frequency and low amplitude waves with reduction in the variability of the EEG and a shift of the rhythmic activity from an occipital predominance to frontal predominance.
- With **increased depth** of anesthesia: EEG depression i.e., EEG shifts towards low frequency with progressive increase in amplitude with burst suppression i.e., periods of isoelectricity in-between periods of activity (figure 7-105).
- With more **progressive increased depth** of anesthesia: There are periods of isoelectricity and finally an isoelectric line occurs.

Effect of Different Anesthetic Agents:

Most anesthetics produce a **biphasic pattern** on EEG i.e., initial activation (at sub-anesthetic doses) followed by dose-dependent depression.

1- Volatile Agents:

- Halothane causes typical biphasic pattern.
- **Isoflurane** is the only volatile agent that causes **isoelectric** line in high clinical doses (1-2 MAC).
- **Enflurane** produces burst suppression at high doses (> 1.5 MAC) and **spike (seizure like) activity**, but does not reach the isoelectric line.
- Desflurane produces burst suppression at high doses (> 1.2 MAC), but does not reach the isoelectric line.
- **N₂O** produces unusual activation as it **increases both frequency and amplitude** (high amplitude activation).

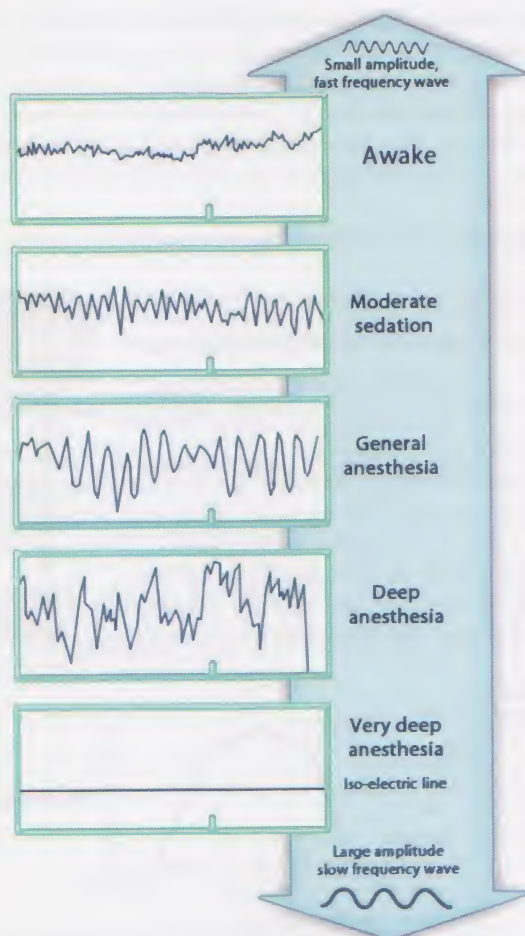


Figure 7-105: EEG changes occurring with different levels of the depth of anesthesia.

2- Intravenous Agents:

- Barbiturates, etomidate, and propofol cause a typical biphasic pattern, burst suppression and isoelectric line in high doses.
- Benzodiazepines cause a biphasic pattern, but without burst suppression or isoelectric line.
- **Opioids** produce **mono-phasic** dose dependent EEG depression.
- **Ketamine** produces unusual activation that consists of high amplitude θ activity followed by very high amplitude δ and low amplitude β activity.

B- Physiological Factors:

1- Hypoxia.

2- Hypercarbia.

Both produce EEG activation at mild stages and EEG depression at severe stages.

3- Hypocapnia.

4- Hypothermia.

Both produce EEG depression only.

5- Sensory stimulation: produces EEG activation only.

Indications (Clinical Uses) of EEG during Anesthesia:**1- Detection of Cerebral Ischemia** during conditions such as:

- Carotid endarterectomy.
- Cardiopulmonary bypass.
- Neurosurgery.
- Head injury.
- Hypotensive anesthesia.
- Drug toxicity.

EEG depression occurs when cerebral blood flow (CBF) reaches $< 15-20 \text{ mL/min/100g}$ of brain tissues.

With more decrease of CBF, progressive depression occurs up to isoelectric line.

Other factors can also cause EEG depression (as above); therefore, it is not specific.

2- Monitoring Depth of Anesthesia.

Especially by: • Power spectral analysis (spectral edge frequency or median frequency, both have moderate accuracy).

- Bi-spectral index: It provides a valid predictor.

3- Titration of Cerebral Protective Agents.

It is performed by EEG to achieve the best cerebral protection by detecting burst suppression or isoelectricity.

4- Management of Status Epileptics:

It allows re-surgical evaluation of epileptic patients before resection of a seizure focus.

III- Evoked PotentialsIt is also called "**The event-related potential or evoked response**".

It is a non invasive assessment of neuronal function by measuring the electro-physiological responses of the central nervous system to a series of specific, repetitive sensory or motor stimuli.

The Response (Evoked Potentials)

The waveform is extracted by averaging several hundred or thousand individual responses. The averaging process removes the random, background electrical activity and leaves only the evoked potential, which is correlated in time to the stimulating clicks.

The waveform formed of voltage versus time shows (figure 7-106):

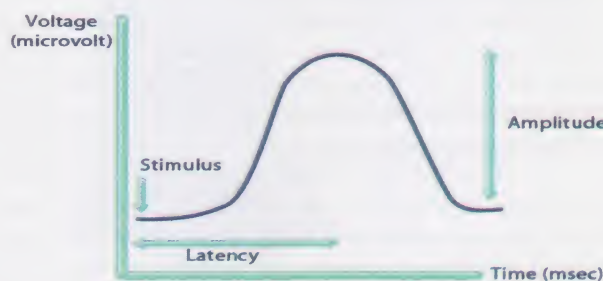
1- **Amplitude:** measured in micro-volts from the baseline to the peak.2- **Morphology:** It is the overall shape of the waveform, described as positive (P) or negative (N).

Figure 7-106: Waveform of evoked potentials

3- Latency: It is the time in milliseconds from the onset of the stimulus to the occurrence of a peak, or time from one peak to another (inter-peak latency).

It is subdivided according to different latencies into:

- **Short latency potentials** (due to **peripheral nerve, spinal cord and brain stem** origin).

Its latency = < 10 ms

It is the **least affected by the anesthetic agents** so it is used generally to **detect ischemia of nervous tissues**.

- **Middle latency potentials** (due to **early cortical** origin).

Its latency = $10 - 100$ ms.

It is less affected, but still sensitive to the anesthetic agents.

- **Long latency potentials** (due to **late cortical** origin).

Its latency or conduction time is long i.e., potentials are recorded after the stimulus by > 100 ms.

It is suppressed by anesthesia. Therefore, it is of **limited value in intraoperative monitoring of ischemia**.

Types (According to the Stimulus):

1- Visual Evoked Potentials

They are produced by repeated flashes of light. They are the most sensitive of all the other types, to the effects of anesthetic agents; so, they are **the least useful for intraoperative monitoring**.

They are used in surgeries involving optic nerve and chiasma, pituitary gland and thalamic tract.

2- Auditory Evoked Potentials (AEPs)

Stimulus: By repeated clicking noise (by ear transducer or headphones) which is applied at a rate of 5-10 per second.

Response: is detected by electrodes over the vertex and the mastoid process (figure 7-107).

They are used in:

- Measuring the **depth of anesthesia** of different anesthetic agents by the **middle (early cortical) potentials** which are **the most promising**, because they are **the most sensitive to the effects of anesthetic agents** as both volatile and intravenous agents cause a dose-related increase in latency.
- Monitoring of **brain stem function** by **short latency (brain stem) AEPs** in:
 - Comatose patients.
 - Surgeries of posterior fossa and brain stem e.g., cerebellar tumor, cerebello-pontine angle, acoustic neuroma.
 - Severe head injury.

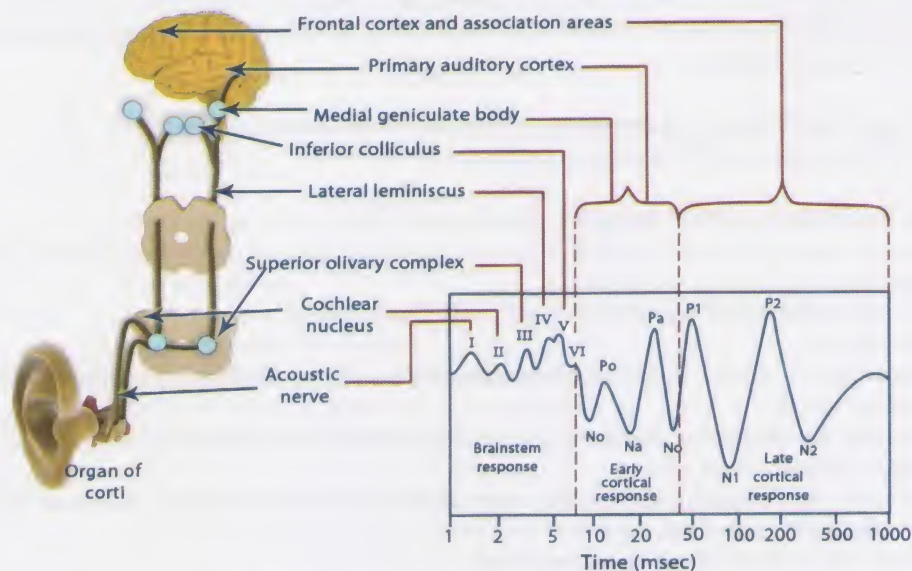


Figure 7-107: Auditory evoked potentials

3- Somato-Sensory Evoked Potentials (SSEPs)

Stimulus: by electric stimulation over a peripheral nerve (e.g., posterior tibial, or median nerve) giving 100-200 ms duration of 1-2 Hz frequency.

Response: is detected by electrodes at various levels (along the neurosensory pathway) from the level of the cortex, epidural space or at the peripheral nerves themselves.

Clinical Uses:

- a- **To assess spinal cord ischemia** as it monitors the **dorsal column** of the spinal cord as in:
 - Scoliosis and corrective spinal surgeries.
 - Resection of spinal cord tumors.
 - Thoraco-abdominal and abdominal aortic surgery.
- b- **To assess cerebral ischemia** in:
 - Carotid endarterectomy surgery.
 - Head injury.
 - Craniotomy.
 - Hypotensive anesthesia.
 - Streptokinase therapy.
 - Intra-cerebral artery aneurysm.
- c- **To assess peripheral nerve ischemia** in:
 - Brachial plexus exploration after injury.
 - Diagnosis of demyelinating diseases as axon demyelination as there will be increased latency, but no effect on amplitude.
 - Spinal disc surgery to monitor spinal roots.
 - Cauda equina syndrome to monitor bladder and rectal sphincter innervations.
- d- **To localize structures in the brain** as:
 - Localization of the sensory-motor fissure (Rolandic fissure) i.e., the gyrus separating the motor and sensory strip, during surgery by phase reversal of the response.
 - Lesions in the thalamus for Parkinson's disease
 - Lesions for pain syndromes.

N.B.: Central Somato-Sensory Conduction Time

It is the time delay (latency) between the action potential (peak) of the brain stem and the action potential of the sensory cortex.

It is normally less than 6.4 ms. If it is prolonged, it indicates:

- Slow axonal conduction.
- Abnormal synaptic delay in the thalamus, cortex or both.
- Cortical dysfunction.

Uses: - Head injury: done at 10 and 35 days post-injury as it correlates well with the outcome.
 - Subarachnoid hemorrhage: used as an index for CBF, so it can monitor developing ischemia.

Factors Affecting SSEPs:

1- Ischemia:

- Mild ischemia causes decreased amplitude > 50% and/or increased latency > 10 %.
- Severe ischemia causes complete loss of waveform.

2- Anesthesia:

- Local anesthetics: (via spinal or epidural) cause loss of SSEPs.
- Volatile agents cause decreased amplitude and increased latency in a dose-dependent manner.
 - Halothane < isoflurane < enflurane.
 - N₂O causes decreased amplitude only (no effect on latency).
- Intravenous agents:
 - Thiopentone, propofol, and diazepam cause decreased amplitude and increased latency in a dose-dependent manner.
 - Etomidate and ketamine cause increased latency and increased amplitude.
 - Opioids cause the least effects.

The short latency SSEPs specifically are the most commonly used intraoperatively to detect ischemia as they are less affected by anesthetic agents.

To obtain the best results during SSEPs monitoring:

- Keep **anesthesia stable before and during** the period of monitoring.
- Use **total intravenous anesthesia (TIVA) better than inhalational** anesthesia.
- **Avoid** the use of **halothane > 0.5%** and **isoflurane and enflurane > 1%**.

3- Physiologic Factors:

- 1- Hypothermia causes increased latency ± decreased amplitude.

- 2- Hyperthermia causes decreased amplitude.
- 3- Hypocarbica (ET CO₂ < 25 mm Hg) causes increased latency.
- 4- Hypoxia causes decreased amplitude.
- 5- Hematocrit (Hct); < 15 % causes increased latency.
< 7 % causes decreased amplitude.

4- Motor Evoked Potentials (MEPs)

It is performed by an electrical stimulation (either **direct electrical current** or **indirect via a magnetic field**) applied to the motor pathway at various levels from the motor cortex (trans-cranial, epidural "electrospinogram" down to the peripheral nerve itself). **Recently, trans-cranial multi-pulse electrical MEPs are used. They are less affected by anesthetic agents.**

It is more sensitive than SSEPs to a reduction of spinal cord blood flow and correlates better with postoperative motor function, because MEPs monitor the **motor pathway in the anterior column of spinal cord** which is more vulnerable to the effects of ischemia during surgery.

IV- Cranial Nerves Monitoring

Stimulus: Electrical current applied to the muscle by bipolar electrodes or hand electrodes except for nerves II and VIII.

Value:

- Monitoring of the motor components is important in surgeries at the **base of the skull, cavernous sinus and posterior fossa** surgery.
- Monitoring of lower cranial nerves (IX, X, XI and XII) is important during resection of **large low brainstem lesions** as their injuries may cause airway collapse and aspiration.
- Monitoring of the **facial nerve** is important, to locate its site, to avoid its injury during posterior fossa surgery (and AEPs) and vestibule surgery.

Response: Electromyography (EMG) of the muscle is recorded and presented visually and audibly.

There are two types of neural activity occurring e.g., with the facial nerve:

1- Brief phasic (bursts) of activity:

It is usually caused by **mechanical stimulation** of the nerve. It indicates that **the nerve** is in the **immediate vicinity** of the surgical field (figure 7-108).

2- Tonic or train activity:

A continuous synchronous motor unit discharges in trains of neurotonic activity lasting up to several minutes. It indicates **potentially injurious** conditions, usually associated with **nerve compression, traction or nerve ischemia** (figure 7-109).



Figure 7-108: Brief phasic activity

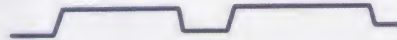


Figure 7-109: Tonic activity

The cranial nerves and related tests are:

- I- Olfactory nerve.
- II- Optic nerve: tested by visual evoked potentials.
- III- Oculomotor nerve: tested by EMG of inferior rectus (motor).
- IV- Trochlear nerve: tested by EMG of superior oblique (motor).
- V- Trigeminal nerve: tested by EMG of masseter and temporalis (motor).
- VI- Abducent nerve: tested by EMG of lateral rectus (motor).
- VII- Facial nerve: tested by EMG of orbicularis oris and orbicularis oculi (motor).
- VIII- Auditory nerve: tested by auditory evoked potentials.
- IX- Glossopharyngeal nerve: tested by EMG of posterior soft palate (stylopharyngeus) (motor).
- X- Vagus nerve: tested by - a special endotracheal tube with electrodes on each lateral surface to test the vocal cords.
or - surface electrode over the larynx (cricothyroid muscle) (motor).
- XI- Spinal accessory: tested by EMG of sternomastoid and trapezius (motor).
- XII- Hypoglossal nerve: tested by EMG of the tongue and genioglossus (motor).

V- Cerebral Blood Flow (CBF) Measurement

It can be measured either:

- a- Direct Methods:**
- 1- Inhalation of 10% N₂O (Kety-Schmidt technique).
 - 2- Intra-carotid injection technique.
 - 3- Inhalation of radioactive xenon technique (xenon computed tomography).
 - 4- Positron emission tomography (PET).
 - 5- Perfusion weighted MRI.
 - 6- Single-photon emission computed tomography (SPECT).
 - 7- Computed tomography perfusion scan (CTP).
- b- Indirect or Bedside Methods:**
- 1- Thermal diffusion flowmetry.
 - 2- Laser Doppler flowmetry.
 - 3- Transcranial Doppler ultrasonography.
 - 4- Intracranial micro-dialysis.
 - 5- Jugular venous oximetry.
 - 6- Brain tissue oxygen monitoring.
 - 7- Near-infrared spectroscopy (Cerebral oximetry).

a- Direct Methods:

1- Inhalation of 10% N₂O (Kety-Schmidt Technique):

Idea:

- The patient inhaled 10% N₂O in air for 10 min. During this period, blood samples are taken at intervals from an artery and the main venous drainage (the jugular bulb). The blood samples are analyzed for N₂O and the results plotted on a graph (figure 7-110).
- The rise in venous concentration lagged behind the arterial concentration whilst N₂O was being taken up by the brain, but by the end of the period of breathing, the venous and arterial concentrations were almost equal, indicating that the brain was fully saturated.
- Amount of N₂O taken by the brain = $M\lambda$

Where M = the mass of the brain.

C = the final concentration of N₂O in blood.

λ = the brain: blood partition coefficient.

- Therefore, according to Fick's principle: The amount of N₂O in the brain ($M\lambda$) = total blood flow during the period of inhalation (Q) x the arterio-venous concentration differences (area A).

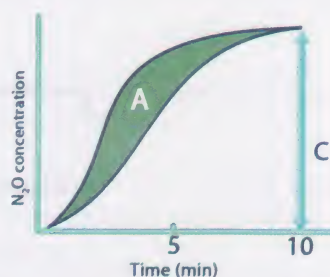


Figure 7-110: Principle of Kety-Schmidt technique

N.B. Measurement of Coronary Blood Flow:

It can be done also by Kety-Schmidt method.

2- Intra-carotid Injection Technique:

Idea:

- The arterial concentration is maintained at zero throughout the period of measurement by using an indicator which is relatively insoluble in blood and soluble in the air, so it is eliminated by one passage through the lungs. The blood flow of the brain can be calculated from the exponential pattern of clearance of the indicator.
- A bolus of ⁸⁵ Krypton or ¹³³ Xenon dissolved in saline is injected into an internal carotid artery and the radioactivity over the head is detected with an array of scintillation counters or gamma camera.

- The bolus will be distributed rapidly throughout the brain tissue and then cleared by the continuing blood flow. Most of the isotope will be cleared from the blood during the subsequent passage through the lungs and the remainder will be distributed widely throughout the body so that the arterial concentration after the bolus has been injected is effectively zero i.e. no recirculation occurs.

- The pattern of clearance in human has an initial steep decline followed by a more gradual fall in radioactivity (figure 7-111). This indicates that the curve is probably representative of two tissue components, one having a relatively fast washout and the other a much slower washout. These may correspond with the flows through white and grey matter.

- By a digital computer program, the fast component i.e. the initial slope can be measured separately which is more important in comparing regional blood flow. This can be obtained by measuring the $t_{1/2}$ (the time taken for the curve to decline to half its initial value).

Then, initial slope = $\frac{0.693}{t_{1/2}}$

- It allows measurement of global and regional CBF.

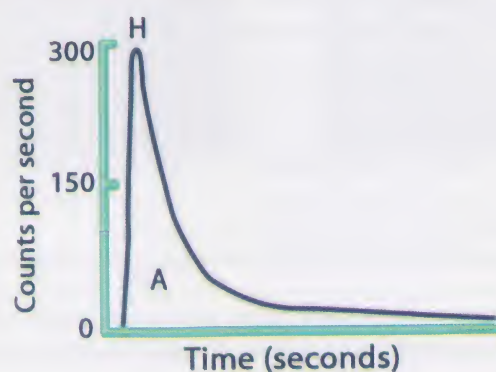


Figure 7-111: ^{133}Xe clearance curve from the brain after a bolus injection into the carotid artery

Measurement of Muscle Blood Flow: can be measured by the same method using radioactive sodium or xenon dissolved in saline which is injected directly into the muscle and the subsequent clearance is detected by an external scintillation detector.

3- Inhalation of Radioactive Xenon Technique (Xenon Computed Tomography):

Idea: The patient breathes ^{133}Xe until the brain tissue is saturated; this is suddenly followed by a 10-minute period of washout, when the patient breathes room air. The washout of the xenon is then detected externally.

4- Positron Emission Tomography (PET):

Idea: PET is used in conjunction with short-lived isotopes such as ^{11}C and ^{15}O to measure the cerebral metabolic rate for glucose and oxygen respectively. It is expensive and needs transfer of the patient to radiology suite due to the cyclotron.

5- Perfusion Weighted MRI:

- When used together with diffusion weighted MRI, the ischemic penumbra potentially can be identified.
- It can assess vascular patency if magnetic resonance angiography (MRA) is added.
- Disadvantages:
 - It is relatively time-consuming when compared to CT scan.
 - It is generally less available and more expensive.

6- Single-Photon Emission Computed Tomography (SPECT):

Idea: It utilizes $^{99\text{m}}\text{Tc}$ as the radioisotope. The tracers cross the blood-brain barrier and localize in the brain tissue in proportion to blood flow. The ischemic area is compared with a presumably normal area in the cerebrum. With administration of acetazolamide to provide a vasodilatory stimulus, functional reserve capacity can be assessed to guide the decision regarding vascular surgery in extracranial as well as intracranial occlusive cerebrovascular disease.

7- Computed Tomography Perfusion Scan (CTP):

Idea: It consists of infusion of iodinated contrast and the concurrent acquisition of images using a helical CT multislice scanner to allow for measurement of changes in tissue attenuation that occur in the brain with time. It allows generation of color-maps of the brain with determining CBF, CBV, global and regional CBF.

b- Indirect or Bedside Methods:

These are noninvasive or minimally invasive methods that can measure CBF continuously; therefore, they can monitor the dynamic changes in flow that occurs with subarachnoid hemorrhage or brain trauma.

1- Thermal Diffusion Flowmetry:

Idea: • These are probes positioned through a burr hole and secured with a metal bolt either over the cortex or inside the parenchyma, and the temperature difference between the neutral plate and the heated element reflects local CBF. It can detect cerebral vasospasm in subarachnoid hemorrhage.

Disadvantages: • It only measures local CBF (area around the probe).

- Probe placement can cause acute brain tissue damage, bleeding, and infection.
- Inaccurate results can occur when the probe is positioned near large vessels or during fever.

2- Laser Doppler Flowmetry:

- It measures local microcirculatory changes (i.e., regional CBF) continuously, assesses autoregulation, CO₂ reactivity, detects ischemic insults, and responds to therapeutic interventions.
- Disadvantages: Patient movement or probe displacement affects readings.

3- Trans-Cranial Doppler Ultrasonography:

- It measures blood flow velocity in the major vessels at the base of the brain via temporal bones. It is not useful in 20% of patients who have temporal bone hyperostosis.
- It is very useful to detect cerebral vasospasm in subarachnoid hemorrhage. It can also confirm brain death.

4- Intracranial Micro-dialysis.

- It measures biochemical markers for occurrence of hypoxia/ischemia. It can identify impending or early onset secondary brain injury.
- These markers include energy metabolites (glucose, lactate, and pyruvate), toxic neurotransmitters (glutamate and aspartate) and tissue damage indices (glycerol and potassium).

5- Jugular venous oximetry.

6- Brain tissue oxygen monitoring.

7- Near-infrared spectroscopy (Cerebral oximetry).

5, 6, and 7 are discussed later.

Clinical Applications:

1- Carotid endarterectomy.

- The ratio of velocity before and after clamping can detect neurological dysfunction.
- It can detect embolism (air or particle) which frequently occurs.
- It can assess the shunt patency and function continuously.
- It can detect post-endarterectomy hyperemia.

2- Cardiopulmonary bypass (CPB).

- It is a sensitive indicator of carotid emboli during CPB.

VI- Monitoring of Cerebral Oxygenation

Physiology

$$\begin{aligned}\dot{D}O_2 &= \text{cardiac output} \times CaO_2 \quad \text{mL/min} \\ &= \text{cardiac output} \times ([Hb \text{ g/dL} \times 1.38 \times SaO_2 \text{ \%}] + [0.003 \times PaO_2 \text{ mmHg}])\end{aligned}$$

Cerebral metabolic rate of O₂ (CMRO₂) i.e., cerebral tissue uptake according to Fick's principle is as follows:

$$\begin{aligned}CMRO_2 &= CBF \times (A-V) \text{ difference of } O_2 \text{ content} \\ &= CBF \times C_{a-j}O_2 \quad \text{where } j \text{ is the jugular vein.} \\ &= 3-3.5 \text{ mL/100 g brain tissues/min.}\end{aligned}$$

Therefore, when SaO₂, PaO₂ and Hb concentration are constant, SjO₂ is \propto CBF/ CMRO₂

Factors that decrease CBF, cause decreased CMRO₂ e.g., hypothermia, barbiturates. They are used in brain protection.

Monitoring of Cerebral Oxygenation: includes:

1- Jugular Vein O₂ Saturation (SjvO₂)

It is measured by a fiberoptic oxy-metric catheter placed in the bulb of the jugular vein which passes retrogradely under x-ray (figure 7-112). It assesses global cerebral oxygenation.

The average normal values of $SjvO_2 = 55-75\%$ which indicates that the **brain tissue extraction ratio is 25-45%**.

If $SjvO_2$ is $> 75\%$, it indicates hyperemia.

$< 50\%$, it indicates cerebral hypoperfusion (due to increased O_2 extraction as in fever or seizures or due to a reduction in O_2 delivery as in vasospasm, hypotension or inadequate CPP).

$< 40\%$, it indicates cerebral ischemia (mainly global).

Disadvantages: ▫ Low sensitivity.

▫ Complications of venous catheter insertion as carotid puncture, hematoma, or thrombosis.

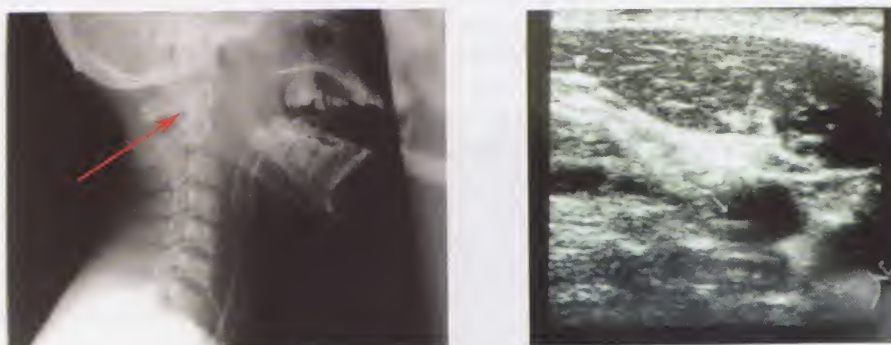


Figure 7-112: The left image is a plain x-ray lateral view neck and the right image is a transverse ultrasound image of the neck showing a fiberoptic oxymetric catheter (arrows) placed in the bulb of the jugular vein.

2- Invasive Regional Brain Tissue PO_2

There are currently 2 direct brain oxygen monitoring systems:

a- Licox monitor: It is a modified flexible Clark-type electrode (miniature Clark electrode) that directly measures oxygen levels.

b- Neurotrend monitor: It is a multi-parameter sensor that utilizes optical fluorescence to measure oxygen and pH.

A cerebral oxygen monitor is placed either intraoperatively or at the bedside, much like a ventriculostomy (see later). Many studies have shown it to be equally as useful as a jugular bulb catheter. The device can either be placed in an ischemic penumbra of a lesion or in an uninjured area of the brain. In the first case, the monitor will yield information that can be used to prevent further ischemia and cell death. In the second case, the device is used as a global indicator of cerebral oxygenation and may be useful in guiding ventilatory management. Cerebral oxygenation monitoring also offers the ability to measure parenchymal temperatures simultaneous to oxygen content, this is of critical importance on using hypothermia or maintaining normothermia.

The average normal values (in normal brain tissues) of $PO_2 = 37 \pm 12$ to 48 ± 13 mm Hg. A value of greater than 30 mm Hg is optimal.

If PO_2 in brain tissues reaches 17-20 mm Hg, it indicates the lowest normal level.

≤ 10 mmHg, it indicates critical range of hypoxic injury.

3- Near-infrared spectroscopy (Cerebral oximetry)

It is discussed above.

Other methods that can assess cerebral oxygenation are

- Conjunctival O_2 tension measurement.
- Trans-cranial Doppler.

VII- Monitoring of the Intracranial Pressure

It is rarely done (not routinely performed), and only restricted to research work, because many risks accompany the measurement of intracranial pressure.

Since there may be obstruction to the flow of cerebrospinal fluid (CSF) from the brain to the spinal cord, it is preferred to measure intracranial pressure rather than spinal CSF pressure. A **catheter connected to a pressure transducer** via a saline-filled tube, is inserted through a **burr hole** (usually under local anesthesia) in ventricles, brain, subdural, extradural, or subarachnoid spaces. It is usually performed by a neurosurgeon. The transducer should be **zeroed** to the same reference level as the arterial pressure transducer (usually the external auditory meatus).

Recently, a catheter-tip transducer (micro-miniature silicon strain gauge) can be inserted directly.

1) Intraventricular Catheter (Ventriculostomy Catheter or External Ventricular Drain)

It is the **gold standard** method for intracranial pressure monitoring and cerebrospinal fluid drainage. It is introduced by Lundberg in 1960. It is the most accurate, inexpensive and reliable method of ICP measurement.

Idea:

A catheter is inserted into the **lateral ventricle** (figure 7-113).

Intracranial compliance may be also measured by injecting 1 mL of saline or withdrawing 1 mL of CSF and observing the change in pressure. If compliance is normal, this should produce a pressure rise of less than 2 mmHg.

A ventriculostomy catheter may be also used to **withdraw CSF to control excessive pressure or for laboratory analysis**.



Figure 7-113: A patient with intra-parenchymal catheter placed in the frontal area for measurement of intracranial tension; the device appears on the left side of the image.

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Disadvantages:

- Sometimes it is difficult to locate the ventricle especially when the brain is swollen; therefore, computerized axial tomography (CAT) scans may be needed.
- The catheter may become obstructed by pieces of brain tissue or by pressure from the surrounding brain.
- It may be associated with brain parenchyma injury.
- Infection may occur; therefore, prophylactic antibiotics may be needed.

2) Intra-Parenchymal Catheter:

A catheter is inserted into the brain parenchyma over the cerebral cortex.

It is very easy and accurate particularly in intensive care unit as they can be inserted by non-neurosurgical staff. Intra-parenchymal fiberoptic and electronic strain gauge systems are available but are more expensive and less reliable than the intra-ventricular catheter.

3) Subarachnoid Catheter (Screw or Bolt)

It is sometimes called **subdural catheter**.

Idea:

It consists of a **hollow bolt** which is screwed through a burr hole made through the fronto-parietal suture line. The dura is incised and the tip of the bolt passes through the dura and its interior is filled with saline so that there is a liquid bridge between the CSF and the pressure transducer. The latter may be fixed directly to the bolt or connected to it by a length of plastic tubing.

Disadvantages:

Hemorrhage, obstruction, or infection as above may occur.

4) Lumbar Subarachnoid Catheter:

Idea:

It measures CSF pressure via a lumbar puncture, but lumbar CSF pressure may not accurately reflect ICP in all circumstances. They may be nearly equal during lateral recumbent position if there is no obstruction.

Disadvantages:

Lumbar puncture may cause tonsillar herniation.

5) Extradural Catheter:

It is not a reliable method of monitoring ICP and has been largely abandoned by many authors.

Idea:

They are different types of transducers which measure intracranial pressure **through the intact dura in the extradural spaces** and avoid the use of a fluid connecting path between the CSF and the transducer.

The transducer is one of the following:

- a- **An external collar** which is inserted through the bone and pushed inwards until the dura bulges into it. **A transducer is then inserted through the collar** until the dura is just flattened. At this point the forces on each side of the dura are equal so that the subdural pressure may be measured.
- b- **A small disc covered by a membrane** which is placed in contact with the dura. The membrane is connected to **a tube which transmits air and two fiberoptic bundles**. The position of the membrane is changed according to the intracranial pressure which is detected by the fiberoptic bundles. The membrane's position is equalized by the air under pressure; therefore, at any point the air pressure and the intracranial pressure are equal.
- c- **A disposable sensor with a thin metal membrane** is placed in contact with the dura. The intracranial pressure is equalized by a pressure from **air flow**, which comes to a chamber above the membrane by one tube and exits through another tube. Therefore, by sensing the pressure in the chamber, it is possible to measure the intracranial pressure.

VIII- Multi-modal Neuro-monitors

1- Intracranial Pressure Spectral Waveform Analysis:

- ICP waveforms are comprised of 3 main components: heart rate pulse, respiratory waves, and slow Vasogenic waves. Analysis of these waves is done now with the assistance of improved computational strategies.
- Pulse amplitude of ICP is dependent on the mean ICP and the pulse amplitude of cerebral arterial blood volume and this pulse amplitude of the waveform is better predictive of clinical severity and outcome in both traumatic brain injury and other pathophysiological changes leading to raised ICP.

2- Cerebrovascular Autoregulation and Pressure Reactivity Index:

- The continuous measurement and comparison of ICP and arterial blood pressure can be used to derive a measure of cerebral autoregulatory capacity called the **pressure reactivity index (PRx)**.
- **Mx** is another index of cerebral autoregulation based on CPP-derived measurements and mean flow velocities from transcranial Doppler.
- **Hemedex thermal diffusion probe** is used for continuous monitoring of cerebral vascular resistance, vaso-reactivity, and cerebral autoregulation.

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IX- Monitoring Depth of Anesthesia

This is done to avoid the risk of awareness.

Guedel (1937) classified the depth of anesthesia into stages and planes of anesthesia which were reliable as long as single inhalational agents were used.

A - Clinical Monitoring:

1- Movement:

It is useful, if muscle relaxants are not used, for example, reflex withdrawal in response to painful stimulus. It is **unreliable** because:

- Movement of patients does not indicate the degree of hypnosis or amnesia, but usually indicates the need for more analgesia.
- Drugs e.g., opioids are effective in suppressing movement intraoperatively although they are not good hypnotics.

2- Autonomic Responses i.e., Sympathetic Over-Activity:

As increased heart rate, arterial blood pressure, pupil size dilatation, lacrimation and sweating.

The PRST scoring system was developed to provide an unbiased assessment of the degree of sympathetic stimulation. A score is allocated to each variable and a total PRST score is calculated based on 4 variables:

Index	Condition	Score
Systolic Pressure (mmHg)	< control + 15	0
	< control + 30	1
	> control + 30	2
Heart Rate	< control + 15	0
	< control + 30	1
	> control + 30	2
Sweating	Nil	0
	Skin moist to touch	1
	Visible beads of sweat	2
Tears	No excess of tears in open eye	0
	Excess of tears in open eye	1
	Tear overflow from closed eye	2

They are **unreliable** because:

- They do not indicate the degree of hypnosis or amnesia, but usually indicate the need for more analgesia.
- The PRST score has not been shown in controlled trials to provide any real benefit in detecting awareness.

N.B.: Not all intraoperative awareness cases are associated with autonomic responses.

- Drugs e.g., thiopentone are effective to produce good hypnosis although they are ineffective in suppressing the autonomic responses, and the reverse is true with opioids as they are effective in suppressing autonomic responses, but they do not produce good hypnosis.
- They are affected by baseline and physiological variables of the patient.

3- Change in Respiratory Rate in Spontaneously Breathing Patients:

As increased rate and shallower depth of respiration are associated with the deep levels of anesthesia.

4- Isolated Forearm Technique:

It is used for detection of intraoperative awareness where one arm is isolated from the remainder of the circulation by inflation of a tourniquet (a pneumatic cuff) above the systolic blood pressure on the upper arm before injection of muscle relaxant into the systemic circulation; therefore, awareness can be detected by responding of the patient to the verbal commands of the anesthetists e.g., squeeze my hand.

It is **unreliable** because:

- A non specific response can occur which may be misinterpreted as consciousness.
- The response may be affected by nerve ischemia caused by the inflated cuff.

B- Electro-Physiological Monitoring

They are used as adjuvant to clinical monitoring.

1- EEG-Unprocessed and Processed: is discussed above.

2- Middle Latency AEPs: is discussed above.

3- Spontaneous Facial (Frontalis Muscle) Electromyogram:

Anesthesia decreases the power of electromyogram reading from the frontalis muscle, but in a non-linear fashion. So, this technique can predict imminent arousal and return of consciousness.

Disadvantages:

- Has a great variability in the response.
- It is affected by neuromuscular blocking drugs which limit its use during anesthesia.

4- Spontaneous Lower Esophageal Contractility (SLEC)

Idea:

The spontaneous rhythmic activity of smooth muscles in the lower 1/3 of the esophagus is decreased in a dose-related manner by halothane, isoflurane and propofol (as it is a smooth muscle, it is not affected by muscle relaxants). It is measured by **an esophageal balloon manometer**.

If a balloon is placed in the esophagus and suddenly inflated, a secondary contraction is induced (provoked), and can be detected lower down the esophagus by a second balloon. This phenomenon is also progressively depressed by increasing the depth of anesthesia, but in contrast to spontaneous contractions, it is the amplitude of the provoked response which is related to the degree of anesthesia therefore:

Esophageal contractility index

= Frequency of **spontaneous** LEC × 70 + Amplitude of **provoked** LEC.

If the index is < 30, deep anesthesia may occur.

If the index is > 70, light anesthesia may occur.

Disadvantages:

- 1- It is **not** sensitive during **alfentanil / N₂O anesthesia**.
- 2- It does **not** predict the response to verbal commands during **propofol anesthesia**.
- 3- It does **not** predict the **hemodynamic** responses.
- 4- It is **affected by**:
 - patient movement,
 - improper manometer placement,
 - smooth muscle relaxants as glyceryl trinitrate,
 - vagotonic drugs as opioids,
 - and • vagolytic drugs as atropine.

N.B.: The usage of esophageal route as a monitor:

- Esophageal stethoscope.
- Tracheo-esophageal echocardiography.
- Esophageal temperature probe.
- Gastric tonometry.
- Spontaneous lower esophageal contractility to assess the depth of anesthesia.
- Esophageal lead of ECG.

5- Respiratory Sinus Arrhythmia:

The degree of respiratory sinus arrhythmia reflects the parasympathetic tone inhibiting the heart via the vagus nerve and brain stem. So, it is continuously analyzed. **Decreased respiratory sinus arrhythmia indicates increased depth of anesthesia.**

(As no single method is considered enough for monitoring the depth of anesthesia, it is still a matter of art to detect the depth of anesthesia and to titrate the doses of anesthetic drugs).

X- Neuromuscular Monitoring**I- Clinical Tests to Assess Reversal of Muscle Relaxants** include:

- 1- Ability to cough or swallow.
 - 2- Sustained eye opening for at least 5 seconds (without diplopia).
 - 3- Sustained head or leg lift for at least 5 seconds (without support).
 - 4- Sustained protrusion of the tongue (without fade).
 - 5- Sustained forceful hand grip (without fade).
 - 6- Ability to **resist removal of a tongue blade from clenched teeth (the most recent and the most sensitive clinical test)**.
- + Tests assessed in unconscious patients:
- Inspiratory force to produce 25 cmH₂O (airway pressure).
 - Vital capacity.
 - Tidal volume.

Disadvantages:

- 1- It needs patient cooperation, so it is not suitable for unconscious patients (except the last three tests above).
 - 2- They are insensitive tests:
- When the clinical tests become adequate, train of four (TOF) ratio is 0.8 i.e., inadequate TOF ratio, so there is a **period of risk between appearance of clinical tests and adequate reversal of muscle relaxant**.

II- Peripheral Nerve Stimulation**Indications:**

A- All patients **receiving muscle relaxants** due to variation in patient's sensitivity to neuromuscular blockade. It is especially indicated in,

- 1- **Prolonged anesthesia** when,
 - Intermediate or long acting muscle relaxants are given.
 - Repeated doses or infusion of short acting muscle relaxants are given.
- 2- Presence of **neuromuscular diseases**.
- 3- Presence of **renal or hepatic diseases**.
- 4- Patients with a history of **sensitivity** to muscle relaxants or poor recovery from them.
- 5- When **poor reversal** of neuromuscular block is encountered **unexpectedly**.

B- **During regional anesthesia** to:

- **Locate the nerves** to be blocked (by a nerve locator).
- **Determine the extent** of sensory block.

Nerve stimulator device: (figure 7-114)



Figure 7-114: A nerve stimulator

Differences between Nerve Stimulator and Nerve Locator:

	Nerve Stimulator	Nerve Locator
Aim	To assess muscle relaxation	To locate a nerve for regional anesthesia
Modes	Single twitch, train of 4, tetany, and double burst stimulation	There is only a single twitch
Amplitude	Should be supra maximal current	Should be minimal current to produce efficient contraction e.g. 0.2-0.5 mA
Stimulus by	Needles or electrodes	An insulated needle

Technique:

Stimulus: It is applied by either:

- Subcutaneous **needle** electrodes; they need a small current (10 mA) as there is no skin resistance.
- ECG silver chloride surface **electrodes**; they need a high current (30-70 mA) as there is skin resistance.

Current Amplitude: **Supra-maximal stimulus** is needed i.e., the strength of the electrical stimulus should be increased until the response no longer increases (i.e., reaching the maximal stimulus). Then it is increased by a further 25% i.e., supra-maximal stimulus. It is a 50 mA current across 1000 Ohm resistance. This supra-maximal stimulus is to ensure consistent excitation of all muscle fibers despite minor variations of skin resistance over time. If a sub-maximal stimulus is applied, some motor units will be unaffected, so changes in the current field due to the skin resistance will change the number of neurons affected and so, the response will be varied and inaccurate.

Stimulus Shape: It should be mono-phasic and rectangular (i.e., square-wave pattern) because a biphasic pulse might cause repetitive action potentials (and repetitive stimulus).

Stimulus Duration (Pulse Width): Increased pulse width causes increased evoked response until the pulse width reaches 0.15-0.2 msec; beyond this pulse width, the evoked response shows little further increase. So, in clinical practice, pulse width should be **0.2 msec**.

Stimulus Site: Stimulating electrodes (needle or surface), both negative and positive electrodes (especially negative electrodes) should be placed **over the course of the nerve tested** to avoid:

- Stimulation of another nerve which causes distorting assessment.
- Direct stimulation of the muscle which underestimates the degree of the block.

Therefore, it assesses the neuromuscular junction and not the muscle itself.

The nerve selected is one of the following:

1- Ulnar Nerve Stimulation (and monitoring adductor pollicis "thumb" muscle).

It is the most commonly used (figure 7-115). One electrode is placed on the radial side of the flexor carpi ulnaris tendon about 1 cm proximal to the wrist skin crease. The other electrode is placed 3-4 cm proximally, or over the ulnar groove on the medial epicondyle of the elbow. This arrangement causes stimulation of the flexor carpi ulnaris muscle and also augments thumb adduction.

If both electrodes are close to the wrist, the polarity of the electrodes is not important, but if one electrode is placed over the elbow, the active (negative) electrode should be placed distally to ensure maximum stimulation of the ulnar nerve.

Advantages of ulnar nerve stimulation:

- **Accessibility** of the ulnar nerve during operations.
- The site of stimulation is on the medial side while the response is on the lateral side, so this **avoids direct muscle stimulation**.
- The adductor pollicis muscle is innervated solely by the ulnar nerve.

Disadvantages:

Muscle groups differ in their sensitivity to muscle relaxants due to:

- Differences in regional blood flow among muscle groups.
- Differences in temperature among muscle groups
- Difference in the density of receptors.
- Difference in the margins of safety at the neuromuscular junction among muscle groups.
- Difference in muscle fiber composition.

Comparing adductor pollicis muscle (a peripheral muscle) and diaphragm (and laryngeal muscles) shows that:

- With nondepolarizing muscle relaxants: the diaphragm and laryngeal muscles have more rapid onset, less intense block, and more rapid offset (mostly due to a higher blood flow).
- With depolarizing muscle relaxants (suxamethonium): both laryngeal muscles and peripheral muscles are similar in onset and offset of paralysis.

Therefore, monitoring of adductor pollicis muscle does not correlate well with the diaphragm and laryngeal muscles.

2- Facial Nerve Stimulation either (figure 7-116):

a- Just as it leaves the stylomastoid foramen near the tragus, 2-3 cm posterior to the lateral border of the orbit to monitor contraction of the orbicularis oculi muscle. This muscle has a **sensitivity to muscle relaxants very similar to muscles of the airway (more than ulnar nerve stimulation)**, but has several **disadvantages**:

- Direct muscle stimulation can occur.
- The response can not be quantified by mechanomyography.

b- Below the lip, to monitor orbicularis oris muscle.

3- Posterior Tibial Nerve Stimulation:

It is done behind the medial malleolus to monitor planter flexion of the big toe and foot.

4- Peroneal and Lateral Popliteal Nerves Stimulation:

They are done to monitor dorsi-flexion of the foot.



Figure 7-115: Ulnar nerve stimulation

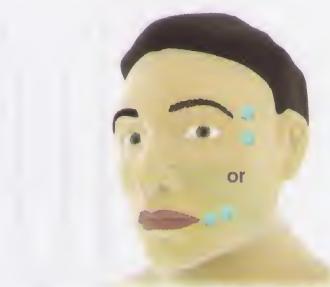


Figure 7-116: Facial nerve stimulation

Mode of Stimulation

1- Single Twitch (ST):

Its duration is 0.2 msec which can be repeated every 10 sec i.e., 0.1 Hz frequency (figure 7-117).

N.B.: Frequency = cycle/sec = Hertz

It is of **limited value** because:

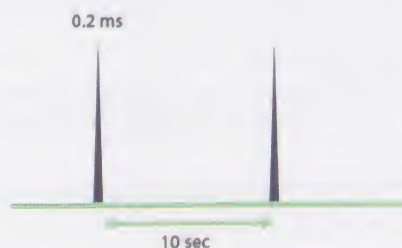


Figure 7-117: Single twitch

1. It is **insensitive** as:

- It does not decrease until 75-80% of the receptors are blocked.
- It disappears completely when 90-98% of receptors are blocked.

So, it covers only a limited range of receptor blocking i.e., >75%.

2. It is **difficult to assess** its fade or its comparison with subsequent twitches by visual or tactile means; therefore, it needs to be measured by more sophisticated means (see later).

2- Train of Four Twitches (TOF): by Ali, Ulting and Gray 1971

It consists of a series of 4 twitches in 2 seconds i.e., 2-Hz frequency. Each twitch is 0.2 msec duration. 10-second gap between each TOF is present. It is considered the **standard method** (figure 7-118).

The ratio of the 4th to the 1st twitch i.e., T₄/T₁ ratio or **TOF ratio**, can indicate presence of fade (i.e., gradual decrease in response on repeated stimulus) which occurs in phase II block of depolarizing muscle relaxants and in the block of non-depolarizing muscle relaxants.

The degree of fade is proportional to the extent of the neuromuscular block as follows:

- At the **unblocked NMJ**, TOF ratio equals 1.0.
- During **phase I block** of depolarizing muscle relaxants, the twitch's height is decreased to the same extent in all four twitches i.e., no fade and **TOF ratio equals 1.0**.
- During **phase II block** of depolarizing muscle relaxants or block of **non-depolarizing** muscle relaxants, T₄ height starts to decrease when 70-75% of receptors are blocked while T₁ is not decreased i.e., there is fade, so **T₄/T₁ ratio is decreased** (= 0.7). This can not be assessed by visual or tactile means.

With more increase of strength of the block:

- 4th twitch disappears **first** (when 80% of receptors are blocked),
- then, • 3rd twitch disappears (when 85% of receptors are blocked),
- then, • 2nd twitch disappears (when 90% of receptors are blocked),
- then, • 1st twitch disappears lastly (when > 90% up to 98% of receptors are blocked).

Clinical relaxation occurs when 75-95% of receptors are blocked.

On recovery from neuromuscular junction block, the 1st twitch appears first (the strongest) then the 2nd then the 3rd and finally the 4th twitch (the weakest) appears.

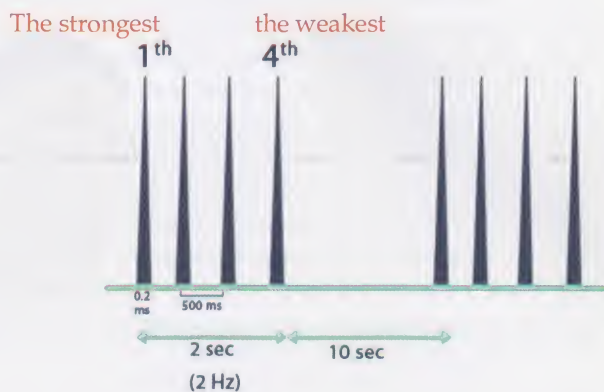


Figure 7-118: Train of four twitches

Value of TOF:

1- To obtain upper abdominal **muscle relaxation** for surgical access, at least the 4th, 3rd and 2nd twitches should be absent i.e., > 90% of receptors are blocked.

2- To **reverse** residual block of nondepolarizing muscle relaxants by an anticholinesterase, at least the 2nd twitch should be visible i.e., < 90% of receptors are blocked.

3- During recovery from muscle relaxants:

- Ali et al in 1970s showed that a TOF ratio of 0.7 correlates with adequate recovery of mechanical ventilatory parameters in most patients and is considered the threshold for adequate recovery from nondepolarizing muscle relaxant drugs.
- Recent data suggest that at TOF of 0.7, signs and symptoms of significant residual paralysis are common. Therefore, **the modern standard** of recovery is now considered to be at **TOF ratio of greater than or equal to 0.9**.

4- TOF is **less painful** than tetanic stimulation, so it is used to detect residual block in an awake patient in the recovery room or intensive care.

3- Tetanic Stimulation:

It consists of sustained stimulus of 50-100 Hz usually lasting 5 seconds (figure 7-119).

Detection of the **tetanic fade** is the **most sensitive mode** for detection of the block of non-depolarizing muscle relaxants. In general, the higher the frequency of stimulation is, the greater the sensitivity of the test i.e., 100 Hz tetany > 50 Hz tetany or TOF > single twitch 0.1 Hz.

It is **intolerable and painful** in awake patients, so it is only used in anesthetized patients.

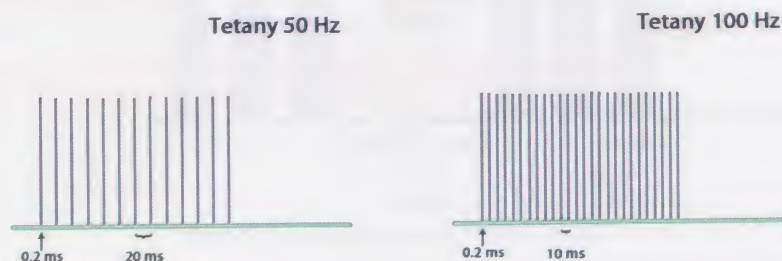


Figure 7-119: Tetanic stimulation

4- Post-Tetanic Potentiation (or Facilitation)

It consists of a single twitch followed by a 5 sec delay, then a burst of 50 Hz tetany for 5 sec (figure 7-120). The effect of a further twitch 3 sec later produces an enhanced effect (potentiation). This occurs with phase II block of depolarizing and block of non-depolarizing muscle relaxants.

In presence of a profound block, repeated single twitches applied after the tetany until the response disappears can be counted. This is known as **the post-tetanic count** which is inversely proportionate to the degree of the block i.e., increased post-tetanic count indicates a low degree of block.

As with tetany mode, it is **painful** in awake patients, thus only used in anesthetized patients.

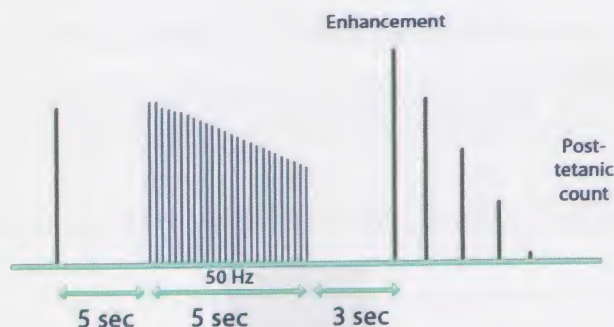


Figure 7-120: Post-tetanic potentiation

5- Double Burst Stimulation (DBS) by Viby-Magensen

It consists of 2 mini-tetanic bursts of stimuli. The first mini-tetanic burst is formed of 3 impulses, each impulse is 0.2 msec and is delivered at 50 Hz frequency and separated from the next impulse by 20 msec interval. The 2 mini-tetany bursts are separated by 750 msec. The 2nd mini-tetany burst consists of 2 (DBS_{3,2}) or 3 (DBS_{3,3}) impulses (figure 7-121).

The ratio of 2nd burst height (amplitude) to the first burst height i.e., D2/D1 ratio can indicate presence of fade as T4/T1 ratio.

D2/D1 ratio has the same sensitivity as T4/T1 ratio if assessed by mechanomyography, but **D2/D1 ratio (fade) is more sensitive (and obvious)** than T4/T1 ratio (and fade) if assessed by visual or tactile means.

It is better **tolerated** in awake patients (than tetany) because:

- It is of a short duration.
- It uses a sub-maximal current stimulus (10-15 mA) without affecting its accuracy.

Response

It is affected by skin and muscle temperatures as:

- Cooling decreases the amplitude of the response due to the increased resistance.
- Heating decreases the amplitude of the response (although it decreases the resistance of electrodes, skin and tissues, it compromises the signal source and increases cutaneous blood flow).

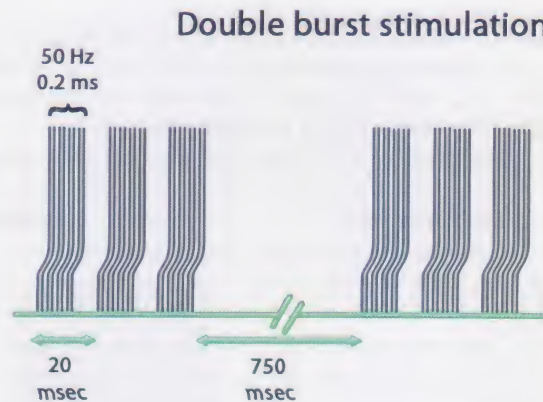


Figure 7-121: Double burst stimulation

Detection of Evoked Responses:**A- Subjective Means (Visual and Tactile Assessments):**

They are the most commonly used during clinical practice, but both are **unreliable**.

DBS is more sensitive than TOF by these subjective means. For visual assessment, the observer should be at an angle of 90° to the plane of the thumb movement.

For tactile assessment, the thumb should be held in full abduction and the observer's finger tip should be placed over the distal phalanx in the direction of movement.

B- Objective Means:

They are reliable methods, but are infrequently used in clinical practice (mainly for research work) because they are expensive and time consuming.

They include:

1) Mechanomyography:

It monitors the response (the force of thumb movement) by a strain gauge transducer.

2) Electromyography (EMG):

It records the electrical activity of the contracted muscle by placing one electrode over the belly of the muscle (close to the neuromuscular junction) and the other electrode over the tendon insertion (figure 7-122).

3) Acceleromyography:

By a thin piezoelectric transducer which monitors the acceleration of the contracted muscle.



Figure 7-122: Electromyography

PART 4: MONITORING OF THE METABOLISM

It includes:

- 1- Temperature monitoring.
- 2- Tissue oxygenation monitoring.
- 3- Indirect calorimetry and Harris Benedict equation.
- 4- Monitoring of blood gases and acid base status.
- 5- Monitoring of fluid and electrolyte status.
- 6- Monitoring of hormonal status.

1- Temperature Monitoring

See before in "temperature" in chapter of "Basic physics for Anesthesia and Intensive Care".

2- Tissue Oxygenation Monitoring

See before in "Monitoring of the respiratory system".

3- Indirect Calorimetry

It is discussed in the chapter of "Intensive (Critical) Care".

4- Monitoring of Blood Gases and Acid Base Status

Recently blood gas analysis and acid base status are assessed by a **blood gas analyzing device**. The device consists of many components which are:

- 1- CO₂ Severinghaus electrode.
- 2- O₂ Clark electrode.
- 3- Co-oximeter.

The above electrodes are discussed in "Monitoring of the respiratory system".

4- H⁺ electrode.

5- Ion sensitive electrode.

- There is an automatic suction control to draw the blood through the channel to be delivered to the measuring electrodes.

- Temperature control is important on measuring O₂, CO₂, and H⁺ because changing the temperature will affect the solubility of gases and affect the degree of dissociation of acids, which in turn will give false results. Therefore, the electrodes and the blood channel are surrounded by a thermal control system to maintain the temperature at 37°C.

Measurement of H⁺ Ions (Hydrogen Electrode)

Idea:

It is an example of an ion-selective electrode. It is formed of 2 electrodes.

a- Measuring electrode:

It depends on **hydrogen ion sensitive glass** which is formed of a special glass material that selectively allows hydrogen ions to pass through, thus producing a potential. The potential depends on the difference of [H⁺] across the glass. The electrode is in contact with a **buffer solution** which is used to maintain H⁺ ions around the H⁺ ion sensitive glass at a constant value; therefore, the potential across the glass is dependent on the [H⁺] in the blood sample with the unknown pH. To measure the potential difference, it is necessary to make an electrical contact with the blood and with the buffer solution (figure 7-123).

Ag/AgCl electrode is connected to the buffer solution and connected to a reference electrode to detect these potential differences.

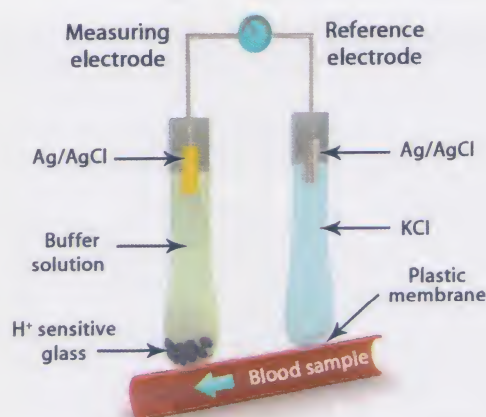


Figure 7-123: Hydrogen electrode

b- Reference electrode:

It is formed of Ag/AgCl electrode and KCl solution which are in contact by a membrane at their tip with the blood sample to avoid contamination.

Both measuring and reference electrodes are connected together, so potential differences between both electrodes can be detected and measured.

This electrode can measure H^+ ions in urine or cerebrospinal fluid.

Disadvantages:

1- **Temperature control at 37 °C** is important, as increased temperature causes increased dissociation of acids and bases which changes H^+ ions. So, the blood sample should be at 37 °C, if not e.g. patient with fever, a correction factor should be used.

2- Arterial blood samples should be **heparinized** and collected **anaerobically**.

3- **Calibration** of the device by 2 buffer solutions containing a fixed concentration of H^+ ions is important before use.

4- The **membranes** should be **cleaned** from any protein materials and should be **without holes** to give accurate readings.

N.B.: Management and interpretation of blood gas analysis are discussed in the chapter of "Acid Base Disturbances".

5- Monitoring of Fluid and Electrolyte Status**Measurement of Blood and Fluid Loss**

See before "Monitoring of the cardiovascular system".

Measurement of Serum Electrolytes (Ion-Selective Electrode)

It is possible to measure the concentration of an ion such as K^+ , Na^+ , Cl^- or Ca^{++} with an electrode which works on the same principle as the $[H^+]$ electrode, but is made of different glass materials which respond specifically to one of these ions.

6- Monitoring of Hormonal Status

The metabolic response to anesthesia and surgery consists of:

- Increased catabolic hormones as cortisol, and catecholamines.
- Decreased anabolic hormones as insulin.

The magnitude of this response is proportional to the extent and duration of surgery. There is increased blood sugar especially in **diabetic** patients and **critically ill** patients, so it is important to assess blood sugar in appropriate intervals by:

- Laboratory tests but results are delayed.
- or • Test strip (Dextrostix or BM test) with a thumb prick. It gives immediate results.

Monitoring of the fetus is discussed in the chapter of "Neonatal Resuscitation".

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Web Sites

- <http://www.asahq.org/publications/AndServices/standards/02.pdf>
- <http://www.pulsion.com>

OPERATING ROOM & INTENSIVE CARE UNIT



Part 1: Operating room & intensive care unit environment

- Operating room
- Recovery room
- Intensive care unit

Part 2: Electrical safety in the operating room and intensive care

- Electric hazards
- Electrocution (Electric shock)
 - Macroshock
 - Microshock
- Safety precautions and measures against electrocution

Part 3: Fires and explosions in the operating room and intensive care

- Definitions and general principles
- The fire triad
- Types of operating room fires
- Safety precautions to prevent fires and explosions

Part 4: Pollution in the operating room

- Risks of chronic exposure
- Methods of measurement of trace anesthetic agent concentrations
- Source of pollution in operating rooms
- Precautions to control pollution in operating rooms

PART 1: OPERATING ROOM & INTENSIVE CARE UNIT ENVIRONMENT

Operating Room

Operating rooms were designed with tiers of wooden benches around the operating table for spectators, thus the term operating theater was introduced.

A Modern Operating Theater (Room) incorporates the following design features:

1- **Environmental controls** as ventilation, temperature, humidity, and noise, to increase the safety in the operating room.

2- **Surgical and anesthetic equipment.**

3- **An operating table** on which the patient is placed in the position required for surgery.

4- **Artificial lighting** appropriate for the requirements of both the surgeon and anesthesiologist.

In addition to: • **A reception area** to accept the patients from the ward and to stay in while they are waiting for the operating schedules.

- **An anesthetic room** (in some hospitals).

- **A recovery room.**

- **A scrub-up area** (to allow the surgeons to scrub up).

- **An area for preparing instruments and sterilizing instruments and towels** (figure 8-1).

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Figure 8-1: A modern operating room

Design

- The ideal shape for the operating room is **circular**, but this is insufficient and most operating rooms are **square or nearly square**.
- The recommended minimum floor area should be **45-58 m²**. Theaters for specialized surgery may require a larger area to accommodate bulky equipment. In the anesthetic room, the minimum floor area should be 17-21 m².
- Outlets for piped gases and electrical sockets must be positioned close to the head of the operating table. They are provided most conveniently by a **boom or stalactite system from the ceiling**. Electrical cables should not lie across the floor.

Cleanliness and Antiseptic Measures

There are 4 zones of cleanliness in the operating theater:

- 1- **Outer zone:** Hospital areas up to and including the reception area.
- 2- **Clean zone:** The circulation area used by staff after they have changed, and the route taken by patients from the transfer bay to the anesthetic room.
- 3- **Aseptic zone:** Scrub-up and gowning area, anesthetic room, theater preparation room, **operating room**, and exit bay.
- 4- **Disposal zone:** Disposal area for waste products and soiled or used equipment and supplies.

Temperature

The temperature in the operating theater and anesthetic room should be **22-24°C**. A higher environmental temperature is required during surgery in neonates or infants.

This temperature is important to decrease the risk of inducing hypothermia in the patient, and in the same time it is comfortable for theater staff. On the other hand, intraoperative hypothermia may offer a degree of neurological protection during some intracranial or cardiopulmonary bypass surgeries.

As a general principle, the comfort of operating room personnel must be reconciled with patients' needs. Controls for temperature (and humidity) should be located within the operating theater.

Humidity

The relative humidity used to be **50-60%** in the past to conduct static electricity especially with the usage of the inflammable agents. Nowadays with the use of the noninflammable agents, this recommendation is no longer important, but static sparks can still damage sensitive electrical equipment or lead to micro-shock.

Pressure

The ambient pressure inside the operating room should be **slightly higher than atmospheric pressure**.

Ventilation

It is usually done by an **air-conditioning system**. In general, air is introduced directly over the operating table, and leaves at the periphery through ducts positioned near the floor level. In the area of the table, 400 air changes per hour are required to minimize the risk of air-borne transmission of infection.

In some theaters like orthopedics, there is a **laminar flow hood** over the operating table bounded by plastic sheets with the anesthesiologist and equipment outside the boundaries.

High-flow systems may cause hypothermia of the patient.

Light

Ceiling-mounting lamps are standard in the operating rooms. It is preferable that they can be positioned directly by the surgeon through a sterile handle. The light should have the following features:

- **The spectrum (color):** should be **similar to that of daylight** to allow good assessment of the skin color of the patient.

N.B.: The color of the décor (walls) should be neutral and uniform.

- **The emitted temperature of the light:** should be 4000-5000 K to be comfortable to the surgeons.
- **The intensity of light:** in the operating room, should be up to 325 lm/m² and should be diffuse to avoid glare, while in the anesthetic room and recovery area, it should be 220 lm/m². Additional spotlights should be available if increased illumination is required for specific procedures.

Noise

Operating room noise has been measured at 70-80 dB with frequent sound peaks exceeding 80 dB, depending on which ventilation system (e.g., laminar flow) and surgical instruments (e.g., power drills and saws) have been used.

Some studies demonstrated that exposure to noise can have a detrimental effect on multiple human cognitive functions e.g., weakness of short-term memory in anesthesia residents.

Recovery Room

- It should be within the clean area. There should be 1.5 places in the recovery area for each operating theater. A greater number is required for surgeries with a high turnover e.g., gynecological or day-case surgeries. Each place requires a minimum floor area of approximately 10 m² and sufficient space must be available to move a patient without disturbing the remainder.
- Each place should have piped oxygen and suction outlets on the wall, with an oxygen flowmeter and a suction apparatus attached to a wall rail. Oxygen is usually administered by a disposable face mask, but each place should have a self-inflating resuscitation bag and an anesthetic mask.
- ECG, pulse oximeter, and blood pressure monitors should be routinely used for every patient.
- In large recovery areas, a mechanical ventilator and anesthetic machine should be available.
- Defibrillator and equipment and drugs for resuscitation should be available in the recovery room.
- At least one nurse is required for each three bed spaces.

Intensive Care Unit (ICU)

All critical care facilities should ideally be proximal to operating theaters, emergency department, laboratories, and imaging suites.

Size:

- The numbers of ICU beds is **generally 1-2% of the total number of acute beds** in the hospital. This figure can be increased according to the activity of the hospital as additional beds are required for regional specialties such as cardiothoracic surgery or neurosurgery. Coronary care units are usually separate units.
- Very large ICU beds (>14 beds) may be divided operationally and allow better concentration of resources.

Patient Areas:

- Space around each bed in an ICU should be greater than an ordinary ward because several nurses may need to treat a patient simultaneously and bulky items of equipment often need to be accommodated.
- Each bed should have a floor space of **26 m² per bed**.

Design

- Floors and ceilings must be constructed to support heavy equipment. Doors must allow for passage of the bulky equipment.
- **Curtains or screens** are required for **privacy**.
- A **wash hand basin** with elbow-operated or infrared operated mixer taps, soap, and antiseptic dispensers should be close to every bed space.
- Some beds should be **isolated for infectious cases**.
- Each bed should have:
 - An oxygen outlet (usually more than 2).
 - A medical air outlet.
 - A high and a low pressure suction outlets.
 - At least 12 electric power sockets (with emergency backup electrical supply) at each bed.
 - A self-inflating resuscitation bag that enable staff to maintain artificial ventilation if the mechanical ventilator or gas supply fails.

Complete monitoring equipment and a mechanical ventilator should be available.

- The bed itself should be able to take many positions.
- The bed areas should have natural daylight.
- Other areas include adequate storage space, separate clean-treatment and dirty/slucide areas, offices, laboratory, seminar room, cleaners' room, staff rest room, staff change and locker room, toilets and shower facilities, and an interview room.

PART 2: ELECTRICAL SAFETY IN OPERATING ROOM AND INTENSIVE CARE UNIT

Anesthesiologists must have at least a basic understanding of the electric hazards, their sources, and their preventions.

Electric Hazards

Excessive electric current through a person may produce:

1- Electrocution (Electric Shock):

It may produce **ventricular fibrillation and death**. There are two types; **macroshock** and **microshock**. Electric shock may occur due to faulty grounding or faulty connection of the electrical devices used in the operating room. See later.

2- Diathermy Burns:

They are more common when there is a high electric current and a slow rate of dissipation of heat energy. For more details, see before "Electricity".

3- Fire and Explosions:

They are common especially with the use of flammable anesthetic agents (rare nowadays), laser, and laparoscopy in surgery. For more details see "Fires and explosions in anesthesia and intensive care".

Electrocution (Electric Shock)

A) Macroshock:

It produces ventricular fibrillation when a current of **100-200 mA** (milliampere) is applied to the skin and passes to the heart. This is called the **ventricular fibrillation threshold**.

Mechanism:

- The current passes between the power station and the hospital along two wires, **the live (hot)** and the neutral, **the neutral wire** being connected to earth at the power station. Mains electric sockets in the hospital provide connections to the live and neutral conductors and also to a third conductor, **the earth or ground wire**, which is connected to earth at the hospital (the third connector is absent in some countries).
- The current flows from one point to another, as there is a difference in the voltage between them e.g., the power station (220 V) and the ground or earth (zero V). Therefore, the circuit is completed.
- If a **grounded person touches the live wire** in the hospital e.g., through a damaged un-insulated cable or through the frame of a device that has developed a faulty connection to the live (hot) side of the power line, an electric circuit can be completed and the electric current passes from the live wire with 220 V to the ground through the body, through the earth, and back to the power station and the person will get an **electric shock**.

Therefore, the rule is to ground the electric equipment and to isolate the patient.

Although earthed equipment is protective, patients are still at the risk of electric shock **even if earthed** as in the following conditions:

- When the feet of the patient touch the stem of a portable lamp or the operating table which is earthed.
- When the patient lies on space blankets (to avoid hypothermia) which are earthed.
- When the patient is connected to a monitor through ECG electrodes which are earthed.
- When the anesthesiologist is in contact simultaneously with the earthed casing of the device and with the patient.

Factors That Increase the Risk of an Electric Macroshock:

The effect of the electric current **depends on**:

1- The Intensity of the Current Flowing:

- If the current is weak e.g., 1 mA, the person will feel a tingling sensation only on touching the live wire of the apparatus.
- If the current increases, pain increases and muscle spasm occurs.
- If the current is strong e.g., 100-200 mA, ventricular fibrillation occurs.

N.B.: The mains electricity supply: - In the United Kingdom is 240 V potential.

- In Egypt is 220 V potential.

- In North America is 110 V potential.

2- The Impedance against the Current:

When the **impedance** against the current is **great**, the **current** will be very **weak** and thus **minimal hazards** occur but when the impedance is very weak, the current will be very strong and serious effects e.g., ventricular fibrillation, occur.

Source of Impedance:

- The impedance of the **skin** is **very small**, about 10 kΩ. It is **not constant**. If the skin is **wet** or there are **needles or cannulas** passing through the skin and the **surface area** of the hand touching the live wire is **large**, the impedance will be very weak and much less than 10 kΩ.

- The impedance of the internal **tissues** is very weak with only a few hundred ohms.

Both have small and negligible impedance; therefore, they are **not protective**.

- The impedance of the standard new **antistatic footwear (shoes)** is **high**, about 100 kΩ.

- The impedance of the **earthed antistatic floor** is **high**, about 25-50 kΩ.

Both have great impedance; therefore, they are **highly protective**.

For example, when a person touches a damaged cable in the operating room, the current will differ according to the impedance as follows:

• If this person is wearing standard antistatic footwear and stands on a dry antistatic floor, the impedance will be great (for example 220 kΩ). Therefore, the current will be weak as follows;

$$\text{Current} = \frac{\text{Potential}}{\text{Impedance}} = \frac{220}{220,000} \times 1000 \text{ mA} = 1 \text{ mA}.$$

So, minimal hazards occur.

• If this person is wearing non-standard footwear and stands on a pool of saline over the floor of the operating room which is in contact with an earthed water pipe (saline is a good conductor of electricity), the impedance will be weak (for example 10-20 kΩ). The saline will bypass the impedance of the antistatic floor. Therefore, the current will be strong as follows:

$$\text{Current} = \frac{\text{Potential}}{\text{Impedance}} = \frac{220}{10,000} \times 1000 \text{ mA} = 22 \text{ mA}.$$

So, serious effects may occur as the current will pass to the earth through the person's body, the footwear, the saline pool and the water pipe especially if the skin is wet.

3- Timing of Current Flowing Through the Heart:

If the current passes through the heart during the vulnerable period of the repolarization of the muscle cells (i.e., with the early T wave of the ECG), the risk of ventricular fibrillation will be great.

4- The Current Density:

A current passing through a small area is more dangerous than the same current passing through a larger area.

5- The Form of Electric Current:

50 Hz alternating current is more dangerous than 1000 Hz direct current.

6- The Duration of Exposure to the Current:

The more the duration of exposure is, the more the risk present is.

7- The Presence of Myocardial Diseases or Dysrhythmias:

They increase the risk of ventricular fibrillation.

B) Microshock:

It produces ventricular fibrillation when a current of **50-100 μA** (microampere) is applied directly to the heart while the patient is earthed e.g., through an intracardiac pacemaker electrode or a saline-filled central venous catheter.

Mechanism:

When a weak current is applied directly to the heart of an earthed patient through an intracardiac conducting material such as:

- A pacemaker electrode
- A saline-filled central venous catheter.
- A temperature- monitoring probe placed in the lower third of the esophagus behind the left atrium (it carries the least risk).

Ventricular fibrillation may occur because the electrode or the catheter touches the wall of the heart and bypasses the resistance of the skin. Blood and normal saline are good electrical conductors.

The electric current may be produced due to:

- **Defective insulation** in the device circuit even with a very weak current.

- **Leakage current** which is the weak current occurring in all electrical equipment due to **inductive and capacitive coupling**, see "Electricity".

These low currents will not produce gross electric shock but may cause microshock, if introduced to the heart directly through an intracardiac electrode or catheter.

The patient is earthed in several conditions as discussed in the macroshock, see above.

Factors That Increase the Risk of Electric Microshock:

They are similar to that of macroshock.

Safety Precautions and Measures against Electrocutation

A) Methods of Protection in the Electric Equipment are classified into:

1- Class I Equipment (Earthed Equipment)

These types of equipment offer basic protection. **Any conducting part that is accessible to the user**, such as the metal case of the device, is connected to an **earth wire**, which becomes the third wire connected via the plug to the mains supply socket.

When a single fault condition such as an insulation fault (short circuit) occurs, the earthed casing of the device becomes connected to the live wire and so the circuit is completed and the **high current will pass from the hot wire to the case to the earth**. This high current will melt a fuse or activate ground fault circuit interrupter.

- **Fuse (circuit breaker)** is included in the circuit so that when a short circuit occurs, the high current will melt the fuse and so the current will be interrupted before a fire or electrocution occurs. The fuse is present in the live and neutral wires. Sometimes, a third fuse is also incorporated in the mains plug.

- **Ground fault circuit interrupter** is included in the operating room electricity system. It can detect very small current leakage (5 mA). When it is activated by the high current, it will interrupt the electric power to all devices that are plugged into the circuit, and may shut off other equipment in the operating room.

- **Both the fuse and ground fault circuit interrupter are not ideal in the operating rooms** because they may interrupt the electricity to life support devices which are essential to the life of the patient.

N.B.: **A single fault condition:**

It is a condition when a single means for protection against hazards in equipment is defective, or a single external abnormal condition is present e.g., short circuit between the live parts and the applied part.

2- Class II Equipment (Double-Insulated Equipment)

All accessible parts to the users are protected by either:

- Two layers of insulation.

- or • A single layer of reinforced insulation.

For example, the casing is made of non-conductive material; therefore, it is not possible that a person touches any conducting part that may become live due to a short circuit. An earth wire is not required in class II equipment. The power cable has only "live" and "neutral" conductors with only one fuse.

3- Class III Equipment (Internally Powered Equipment)

These devices have their own power supply at a very low voltage produced from either:

- Batteries, located within the equipment.

- or • A secondary transformer situated some distance away from the device.

This type of equipment does not need an electrical supply exceeding 24 V AC or 50 V DC.

Although the risk of electric shock may still be present, the risk of contacting the mains electricity on grounding is avoided.

B) Isolated Patient Circuits (Floating Circuits)

Monitoring equipment such as an ECG monitor is connected to the patient through a cable and electrodes where the skin impedance is reduced by the jelly in the electrode. This decreases the protection provided by the skin against the electric shock. Therefore, most equipment use an **isolated patient circuit (floating circuit) that connects the patient to a secondary circuit away from the mains supply**.

The electric current of the equipment is divided into two parts:

- **A mains part**, which contains a power supply driven directly by the mains.

- **An isolated part**, which is separated from the mains part by an electric barrier. This circuit is not earthed and it is produced by an isolation transformer. Thus, if the patient comes in contact with the live circuit of the secondary isolated part and ground, no current is transmitted to the ground. It is intended to provide protection to the patient from the mains supply and decrease the flow of mains leakage currents in the patient circuit.

C) Leakage Current Standards:

Equipment is also classified according to the **permitted leakage current** allowed in case of presence of a single fault condition such as reversal of the neutral and live wires or disconnection of the earthed wire into:

1- Type B Equipment:

This may be class I, II, or III. This equipment is designed to have low leakage currents, even in fault condition such as 0.5 mA for class I and 0.1 mA for class II.

"B" indicates that the equipment is safe to be in **contact with the body surface**

It may be connected to the patient externally or internally, but it is not considered safe for direct connection to the heart.

The equipment may be provided with defibrillator protection.

2- Type BF Equipment:

It is similar to type B.

"B" indicates that the equipment is safe to be in **contact with the body surface**.

"F" indicates that the equipment has a **floating circuit**.

In this equipment, the leakage current allowed through the body in case of presence of a fault is **less than 0.5 mA**.

It is safer than type B but still not safe enough for direct connection to the heart. The equipment may be provided with defibrillator protection.

The above two values are different according to the type of the device used.

3- CF type Equipment:

"C" indicates that the equipment is safe to be in **direct contact with the cardiac muscle**.

"F" indicates that the equipment has a **floating circuit**.

In this equipment, the leakage current allowed through the intracardiac connection in case of the presence of a fault is **less than 50 μ A**. They may be provided with defibrillator protection.

There are many symbols which are present on the case of the equipment (figure 8-2).

Class II equipment	Type B equipment	Type BF equipment	Type CF equipment
Attention 		Protective earth 	Functional earth
Additional protective earth 	Equipotentiality 	Drip proof, Splash proof Water tight 	Off, On
Anesthesia-proof equipment 	Anesthesia-proof equipment category G 	Conformity according to Council of Europe Directive 93/42/EEC concerning medical devices 	

Figure 8-2: Equipment symbols

D) Ungrounded Power Systems

• The electric power supply in the operating room should be ungrounded (isolated). The grounded power supplied by the electric company is converted to ungrounded isolated power by means of an **isolation transformer** in the operating room which uses **electromagnetic induction to induce current in the**

secondary ungrounded circuit. Therefore, there are two circuits in the operating room; a primary grounded circuit to which the casing of the equipment is connected and a secondary ungrounded circuit.

- **The advantages of ungrounded power supply:** if a single short-circuit is present and a live wire is unintentionally contacted by a grounded patient, current will not flow through the patient, as there is no circuit back to the secondary transformer, and so the electric current will not produce electrocution or power interruption. **If two faults** occur, shock may occur. Therefore, presence of one fault necessitates removal of the device to avoid the risk of shock if another fault occurs.

- **A line isolation monitor** is used to monitor the integrity of the isolated power system and alarms when they are no longer isolated. The line isolation monitor is set to alarm when the leakage current is more than 2 mA or the ground impedance is less than 25 ohm. This occurs when a faulty device is connected and plugged in the operation room circuit. Therefore, if the alarm is activated, the last piece of equipment that was plugged in is suspected to be faulty, and should be removed from service until it is replaced or repaired (figure 8-3).

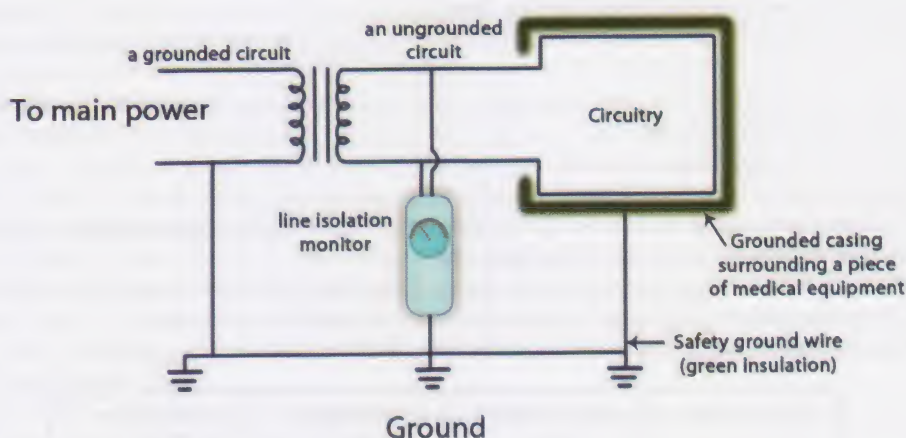


Figure 8-3: An isolation transformer and monitor

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E) Isolation of the Patient:

Everything in the operation room should be grounded except the patient who should be isolated and not earthed.

PART 3: FIRES AND EXPLOSIONS IN THE OPERATING ROOM AND INTENSIVE CARE UNIT

Definitions and General Principles

Oxidation: is a chemical reaction between **any molecule** and an oxidizing agent as **oxygen or nitrous oxide**. Most of oxidation reactions **liberate heat** i.e., exothermic reactions.

Combustion: is a chemical oxidation reaction between a combustible agent e.g., **fuel molecules** and an oxidizing agent as **oxygen or nitrous oxide**. The reaction is **initiated by** activation energy e.g. a **small spark** and it gives reaction products, as CO_2 and H_2O that are the final products, and energy. In the combustion, **the oxidation process is so fast** that the mixture heats up markedly. When the **heat of the reaction increases up** to a certain level, it becomes sufficient to act as activation energy and the reaction becomes **self-sustained**.

Factors Affecting Combustion

The concentration (proportion) of the combustible agent and the oxidizing agent is the main factor.

- At a certain concentration or proportion of the fuel and oxidizing agent as O_2 , all the fuel and O_2 molecules are transformed into CO_2 and H_2O i.e., the combustion is complete and the reaction is violent where explosion occurs. The mixture is said to be at the **stoichiometric concentration**.

- If the concentration of the mixture differs, the reaction becomes less violent and fire occurs.
- When one component is greatly in excess of the other, the mixture cannot be ignited at all. The limits, outside which the mixture will not burn, are known as **the flammability limits**. There are upper and lower flammability limits. Beyond these limits ignition never occurs (figure 8-4).

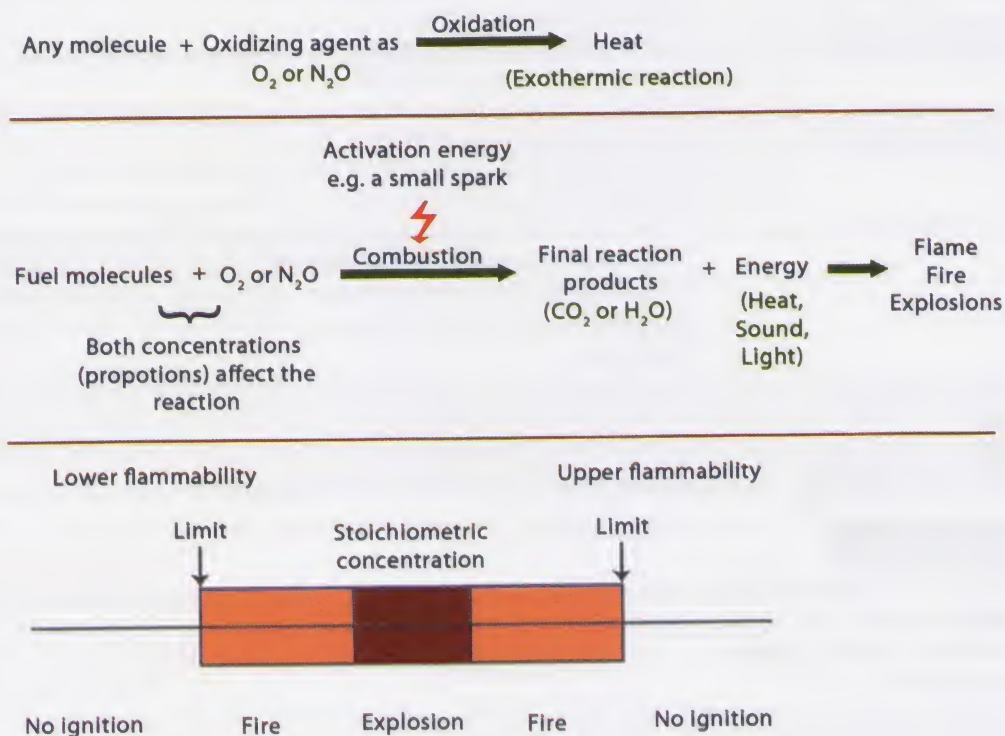


Figure 8-4: Combustion

Differences between Fire and Explosion

Fire	Explosion (Conflagration, Detonation)
<ul style="list-style-type: none"> • It occurs at a concentration near the flammability limits. Fire is maximal when the fuel concentration is near the stoichiometric concentration. The mixture in which fire occurs is said to be flammable. 	<ul style="list-style-type: none"> • It occurs at the stoichiometric concentration.
<ul style="list-style-type: none"> • The combustion reaction occurs at a slow speed. 	<ul style="list-style-type: none"> • The combustion reaction occurs at a very fast speed which may be 8 times the speed of sound.
<ul style="list-style-type: none"> • The temperature is relatively low, about several hundred degrees Celsius. 	<ul style="list-style-type: none"> • The temperature is very high, about 3000°C.
<ul style="list-style-type: none"> • It generates very small pressure; so, the pressure is close to the atmospheric pressure (1 bar). 	<ul style="list-style-type: none"> • It generates very high pressure; so, the pressure is about 25 bar.
<ul style="list-style-type: none"> • Less light is produced. 	<ul style="list-style-type: none"> • More light is produced.
<ul style="list-style-type: none"> • Minimal sound waves are present. 	<ul style="list-style-type: none"> • Maximal sound waves are present.

Flame: is combustion associated with emission of light and heat. There are two types:

- Static flame:** The flame does not spread but is confined to a particular site e.g., the tip of a candle.
- Self-propagated flame:** The flame spreads throughout the combustion mixture at a certain speed.

For example;

- Cyclopropane in 100% oxygen:
 - The lower flammability limit of cyclopropane is 2.5%.
 - The upper flammability limit of cyclopropane is 63%.

- The stoichiometric concentration of cyclopropane is 18% where explosion may occur.
- Cyclopropane in 21% oxygen (air):
 - The lower flammability limit of cyclopropane is 2.5%.
 - The upper flammability limit of cyclopropane is 63%.
 - The stoichiometric concentration of cyclopropane is 4.3% but explosion does not occur.
- Ether in 100% oxygen:
 - The lower flammability limit of ether is 2%.
 - The upper flammability limit of ether is 82%.
 - The stoichiometric concentration of ether is 14% where explosion may occur.
- Ether in 21% oxygen (air):
 - The lower flammability limit of ether is 2%.
 - The upper flammability limit of ether is 34% with risk of cool flames.
 - The stoichiometric concentration of ether is 3.4% but explosion does not occur.
- Ethyl alcohol in 21% oxygen (air):
 - The lower flammability limit is 3%.
 - The upper flammability limit is 19%.
 - The stoichiometric concentration is 6% which is the saturated vapor pressure of ethyl alcohol where fire still can occur, but explosion does not occur.

N.B.: When liquid ether is split and produces a high concentration of ether vapor near the floor, the concentration of ether may approach the upper flammability limit in air and if the ether is ignited, **cool flames** occur, which are invisible and with low temperature giving rise to acetic acid and acetaldehyde rather than CO_2 and H_2O . Cool flames may burn the anesthetic breathing systems.

The Fire Triad

For a fire to occur, 3 elements must come together at the same time. They are known as the fire triad. They are: - Fuel.

- A source of ignition or heat.
- An oxidizer.

1- Fuel (Flammable Materials)

They are present in the operation room. They are organic materials such as:

- Flammable anesthetic agents such as **cyclopropane and ether**, which are no longer used in modern anesthetic practice. Ether still may be used to degrease the patient's skin.
- **Methane and hydrogen gases in the patient's gut**, which may be ignited by diathermy when the gut is opened.
- **Oil and grease** that may ignite spontaneously in the presence of high pressure of oxygen, nitrous oxide or compressed air supplies. Oil and grease should not be used on reducing valves and cylinders.
- **Ethyl alcohol** used to clean the patient's skin.
- **Ethyl chloride** used as a local anesthetic spray.
- **Paper drapes, plastics, gauze dressing, endotracheal tubes, and linens** used inside the operating room.
- **The tissues of the patient** themselves that act as a fuel.

2- A Source of Ignition or Heat:

In a mixture of a combustible agent and oxygen, the molecules are normally kept apart by repulsive forces. For the mixture to burn, the molecules must be brought close enough to react together. This can be achieved by increasing the speed with which the molecules collide which can occur by increasing the temperature of the mixture locally. Therefore, a source of heat is needed.

The temperature at which ignition occurs is called the **ignition temperature**.

The quantity of heat energy required to start the ignition is called the **activation energy**. It is about 1 μJ with 100% oxygen and about 100 μJ with air at the stoichiometric concentration.

Sources of ignition include:

- **Direct heat** e.g., open flame, electrocautery, hot bulbs, laser beam, or a fiberoptic light cord.
- **Electric sparks** e.g., from diathermy, switches, plugs, faulty connections (short circuits), and electric equipments.
- **Static electricity** as that generated from rubber e.g., rubber mattresses, wool, nylon, plastic and other synthetic materials which are non-conductive materials.

3- An Oxidizer (Supporting Atmosphere)

Oxygen, nitrous oxide, or air acts as an oxidizing gas in the operating room which supports the combustion

- It is clear that the range at which flammability occurs is less in presence of air and the possibility of explosion is rare. The inert nitrogen molecules in air not only absorb some of the energy produced but also do not take part in the reaction; therefore, the reaction is much less violent and no explosion occurs.
- By increasing the concentration of oxygen, the combustion will be more violent and explosion may occur.
- Presence of nitrous oxide with the oxygen makes the reaction more violent and the explosion more severe because when a fuel burns in nitrous oxide, more heat is produced than when the fuel burns in oxygen alone.

Types of Operating Room Fires

A) Fires in the Patient:

1- Laser:

a- Upper Airway Surgery:

For more details see "light and optics" in chapter of "Basic Physics for Anesthesia & Intensive Care".

b- Lower Airway Surgery:

The Nd: YAG laser fiber passes inside the trachea through the suction port of the fiberoptic bronchoscope which passes via either an endotracheal tube or a rigid metal bronchoscope. The precautions are nearly the same as upper airway laser surgery but there is no special tube for this type of surgery.

2- Electrocautery:

a- During Tonsillectomy in a Child:

In children, uncuffed tracheal tubes are used which allow leakage of O₂ and N₂O around the tube; therefore, when the electrocautery is used, fire may occur.

It is recommended to:

- use O₂ and air mixture, and keep O₂ concentration as low as possible.
- use wet pledgets around the tube by the surgeon. If the pledgets dry out, they can be a source of fuel for a fire.

b- During Laparoscopic Surgery:

After 30 minutes of O₂ and N₂O anesthesia, the N₂O (an oxidizing agent) diffuses into the abdominal cavity. If the surgeon injures the gut, methane and hydrogen gases (a fuel) escape to the abdominal cavity, so when electrocautery (a spark) is used, combustion may occur. This becomes more severe if N₂O is used as an insufflating gas.

It is recommended to:

- avoid the use of N₂O to produce pneumoperitonium in laparoscopic surgery. Therefore, CO₂ is more preferred because it does not support combustion and has a greater solubility in blood than nitrous oxide, thereby, decreasing the risk of gas embolism.
- avoid the use of N₂O during anesthesia in these surgeries.

c- During Tracheostomy:

If electrocautery is used during tracheostomy, ignition of the endotracheal tube may occur especially if O₂ is given to the patient.

It is recommended to:

- decrease O₂ concentration.
- avoid the use of electrocautery and use a scalpel or a scissor instead.

B) Fires on (Outside) the Patient:

1- During Monitored Anesthesia Care (MAC) for Head and Neck Surgery:

- During head and neck surgeries, the patient receives O₂ by a face mask or a nasal cannula. The surgeon then drapes the field such that there is a build up of 100% O₂ under the drapes and in close proximity to the operative site. Therefore, when the electrocautery or the laser is used, a fire can be started.

- It is recommended to:

- decrease the sedatives to allow using less concentrations of O₂.
- avoid unnecessary insufflation of oxygen under surgical drapes especially after the routine use of pulse oximetry.

- Arrange the drapes so that the O_2 does not build up underneath the operative site. They can be arranged in a fashion like an open tent so the oxygen will be diluted with air. Because the oxygen is slightly heavier than room air, it will tend to flow towards the ground.
- Discontinue O_2 several minutes before the surgeon uses the laser or the electrocautery, but this may be impractical if they are used frequently.

2- During Skin Preparation Using Isopropyl Alcohol:

Isopropyl alcohol is a volatile solution (a fuel). It can pool in certain areas and remain liquid for a considerable period of time. It also vaporizes forming a vapor. In O_2 enriched atmosphere, both liquid and vapor are highly flammable.

Safety Precautions to Prevent Fires and Explosions

To prevent fires and explosions, it is necessary to isolate one component of the fire triad.

1- Avoidance of the Use of Flammable Anesthetic Agents:

- Nowadays, the use of inflammable agents as ether and cyclopropane is rare. All the modern anesthetic agents are non-flammable and non-explosive at air or O_2 such as halothane, enflurane, isoflurane, Desflurane, and sevoflurane. All these anesthetics are fluorinated. The combination of carbon atom with fluorine atom (C-F bond) decreases flammability.
- If ether is still used: the following recommendations are needed;
 - Avoid the use of sources of ignition such as diathermy or laser.
 - Use the low-flow or closed circuits.
 - Allow good ventilation of the operating room.
 - Use a well functioning scavenging system.

2- Classification of Equipment According to the Zones of Risk:

A flammable anesthetic mixture (containing O_2 and N_2O) is normally contained within the breathing system, the patient's airway, and anesthetic apparatus and equipment attached to it, but the mixture may pass into the room air either as a discharge of expired gas or from a leak. Two zones are present:

- **5 cm zone** around the discharge or leak where the concentration of anesthetic mixture is high and the oxidizer agent is O_2 and N_2O .
- **25 cm zone** around the first zone where the concentration of anesthetic mixture is low and the oxidizer agent is air.

Equipment are classified into:

• Category APG Equipment:

They are designed and constructed in such a way as to avoid the ignition of a flammable anesthetic mixture with O_2 or N_2O . They are marked with the letters APG on a green band.

• Category AP Equipment:

They are designed and constructed in such a way as to avoid the ignition of a flammable anesthetic mixture with air. They are marked with letters AP on a green circle. These equipment should not be used in the first zone.

Equipment which do not belong to either of these categories may be marked as equipment not suitable for use in the presence of a flammable anesthetic mixture with air or with O_2 and N_2O .

3- Prevention of Electric Sparks:

- Periodic checking of electric equipment and connections.
- Use of spark-proof mercury switches.
- Use of dry battery for endoscopes.

4- Prevention of Static Electricity:

This is performed by the use of **antistatic materials** inside the operation rooms. The antistatic materials contain carbon which conducts the static electricity and allows the static charges to drain away (hence the black color of anesthetic breathing tubes, bags, masks, and wheels of tables).

The antistatic materials should have a resistance between 50-10 000 $k\Omega/cm$. Resistance, if too low, is undesirable as it could increase electrocution risks, whereas if too high it would allow electrostatic charges to build up.

For example:

- Antistatic floors.

- Antistatic breathing circuits, bags and masks. In modern anesthesia practice, due to the use of non-flammable anesthetics, different colors of breathing circuits, bags, and masks are now present which are not antistatic.
 - Antistatic clothes e.g., cotton. Avoid the use of synthetic materials and wool.
 - Antistatic wheels of the operating table, anesthetic machines and fluid supports.
 - Antistatic rubber-soled shoes which are worn by the staff (figure 8-5).
 - The relative humidity of the operating room should not be less than 50%.
 - Grounding (earthing) of electric equipment to conduct static charges to earth.
- N.B.: Most of these recommendations are disregarded in the modern anesthetic practice.



Figure 8-5: Antistatic rubber-soled shoes

5- Fire-Fighting Equipment (Fire Extinguishers)

They should be always available and their location should be known by all the operating room staff. There are 3 classes of fire extinguishers:

- Class A: are used for wood, paper, cloth, and plastics.
- Class B: are used for flammable liquids or grease.
- Class C: are used for energized electrical equipment.

For example:

- Halon fire extinguishers: can be used for the 3 classes. They do not damage electronic equipment.
- CO₂ fire extinguishers: can be used in the 3 classes. They may damage the electronic equipment.
- Pressurized water: can damage the electronic equipment.

6- Precautions during Laser, Tonsillectomy, Laparoscopic, and Head and Neck Surgeries

They are discussed above.

Extinguishing a Fire

To extinguish a fire, one component of the fire triad should be isolated.

- 1- **Remove the oxidizer agent** by disconnecting the O₂ or the circuit from the patient.
 - 2- **Remove burning drapes** quickly as possible, and once on the floor, they can then be extinguished.
- N.B.: Impervious paper drapes will repel water; therefore, attempting to throw water on these burning drapes would be useless as the fire will actually burn on the underside of the drapes.
- 3- Use a **fire blanket** which is effective.
 - 4- **Sprinkler system** is important inside the operating room, but they are **ineffective** and are frequently not activated in the operating room because:
 - They are rarely located over the operating room table.
 - They are heat activated but operating room fires tend to give off a lot of smoke and toxic products but insufficient heat to activate sprinklers.
 - 5- **Halon fire extinguishers** are used.

PART 4: POLLUTION IN THE OPERATING ROOM

The main source of pollution inside the operating rooms is the inhalational anesthetic agent. Although the patient is exposed to very high concentrations of these agents without detrimental effects but the operating room personnel are exposed to a very trace concentration for very long times throughout most of their professional life.

The anesthesiologists are more exposed than any other operating room personnel as they are more close to the anesthetic machines than any one else.

The small concentrations of inhalational agents are expressed as part per million (ppm).

The Maximum Allowable Levels of Exposure are:

- In USA; 25 ppm for N₂O.
2 ppm for volatile agents if used alone.
0.5 ppm for volatile agents if used with N₂O.
- In UK; 100 ppm for N₂O.
50 ppm for enflurane and isoflurane.
10 ppm for halothane.

Risks of Chronic Exposure

1- Nervous System:

Dentists and dental assistants may be at an increased risk of **neurological disease** from exposure to N₂O.

2- Reproductive System:

Female anesthesia personnel and wives of male anesthesiologists who work in the operating room may be at a slightly increased risk of **spontaneous abortion** and of having offspring with **congenital abnormalities**.

3- Gastrointestinal System:

Both male and female anesthesia personnel may be at a higher risk of **hepatic disease** as serum hepatitis which is not totally explained.

4- Renal System:

Female operating room personnel may be at an increased risk of **renal disease**.

5- Immune System:

Female anesthesia personnel may be at a slightly increased risk of **cancer** and **infections**.

6- Impairment of Professional Performance.

N.B.: **None** of these risks have been **definitively proved** and **laboratory studies** have **failed to link** trace concentrations of modern anesthetic agents to mutagenic, carcinogenic, or teratogenic consequences in animal models.

Methods of Measurements of Trace Anesthetic Agent Concentrations

- 1- Gas chromatography.
- 2- Mass spectrometry.
- 3- Infrared analyzers: are the most practical because:
 - They are relatively inexpensive.
 - They are portable, battery operated and easy to use.
 - They have rapid response time and give continuous measurement, so different locations can be analyzed quickly.
 - They are accurate and reliable.

Sources of Pollution in Operating Rooms

- 1- **Leakage of anesthetic gases and vapor** from cylinders, pipelines, flowmeters, vaporizers, and anesthetic breathing systems.
- 2- **Faulty techniques:** as:
 - Poor fitting of the facemask.
 - During filling of vaporizers.

- Premature flow of anesthetic gases e.g., before placement of facemask or endotracheal intubation.
- 3- Other used materials** as volatile skin-cleaning fluids, aerosol sprays e.g., iodine, plastic skin dressings, or ethyl chloride.
- 4- Poor ventilation of the operating room.**
- 5- Absence or malfunction of the scavenging system.**

Precautions to Control Pollution in Operating Rooms

- 1- Periodic maintenance of anesthetic equipment** for detection and correction of leaks.
- 2- Proper anesthetic techniques:** as - Proper fitting of facemask.
 - Careful filling of the vaporizers.
 - Turning off of N₂O cylinders and vaporizers when not in use.
- 3- Adequate ventilation of the operating room by air conditioning:** There are two types of air conditioning systems:
 - a- **Recirculating system:** The air is taken by the air conditioner and re-circulated back to the operating room. It is less effective in removing the waste anesthetic gases.
 - b- **Non-recirculating system:** The air is delivered to the operating room and the waste air is exhausted to outside. It is more effective in removing the waste anesthetic gases.
- 4- Usage of scavenging system.**

Further Readings

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Web Sites

- <http://www.ecri.org>
- <http://www.nfpa.org>

AIRWAY MANAGEMENT

9

- Secure a patent airway
- Laryngoscopy and intubation:
 - Endotracheal tubes
 - Rigid laryngoscopes
 - Technique of intubation
 - Complications of laryngoscopy and intubation
 - Difficult airway and intubation
 - Extubation
- Management of the obstructed airway
- Recent airway devices and techniques

Airway management (maintaining patency of the airway) is one of the most important tasks for anesthesiologists and physicians in intensive care units. Difficult or failed airway management is the major cause of anesthesia-related morbidity and mortality.

Secure a Patent Airway

A) Mechanical Maneuvers:

They are done to remove obstruction produced by falling of the tongue (posterior placement).

1- Chin Lift-Jaw Thrust Maneuver:

It is performed by placing fingers behind the angle of the mandible on both sides and lifting the mandible forward and upward until the lower teeth or gum are in front of the upper teeth or gum. It can be done with **the neck in the neutral position**, so it can be performed if a cervical spine injury is suspected (figure 9-1).

2- Neck Lift-Head Tilt:

It is performed by tilting the head back with extension of the neck. One hand (palm) is placed on the patient's forehead applying pressure to tilt the head back while lifting the chin with the forefinger and index finger of the opposite hand. It is **contraindicated if cervical spine injury is suspected** (figure 9-2).



Figure 9-1: Chin lift-jaw-thrust



Figure 9-2: Neck lift-head tilt

B) Airway Devices:

Indications:

- They relieve obstruction above the laryngopharynx caused by **loss of upper airway muscle tone (e.g., genioglossus)** as in anesthetized patients. This leads falling of the back of the tongue and the epiglottis against the posterior wall of the pharynx. Therefore, insertion of an artificial airway creates an air passage between the tongue and the posterior pharyngeal wall (figure 9-3).
- They aid in **removal of secretions** from the posterior pharynx.
- Oral types **prevent biting of the tube by the patient** during awakening from anesthesia.



Figure 9-3: Loss of airway muscle tone in an anesthetized patient causing airway obstruction (left), inserted oropharyngeal airway (middle), and inserted nasopharyngeal airway (right)

Types:

I- Oropharyngeal Airway:

- There are many sizes 000, 00, 0, 1, 2, 3, and 4. The distance between the tip of the nose and the earlobe (or the distance between the teeth and the angle of the jaw) approximates the correct length of an oral airway.
- The airway is inserted into the mouth with the curve pointed toward the skull then rotated 180° once the soft palate is reached.
- It may cause cough or even laryngospasm, if the laryngeal reflexes are intact in awake or lightly anesthetized patients.
- There are many types:
 - **Guedel airway** is the most common (figure 9-4).
 - **Berman airway** (figure 9-5). It is also available in color-coded models.
 - **ChaoAirway** (figure 9-6) is formed of a rigid outer tube that serves as a conduit for and protects the inner flexible tube from biting. Both outer and inner tubes are made separately and assembled together for use.

Cuffed Oro-Pharyngeal Airway (COPA): is a modified conventional oral airway with a large oral cuff at its distal end. It can be connected to breathing circuits to supply anesthesia because it has the standard 15-mm connector (figure 9-7).



Figure 9-4: Guedel airways



Figure 9-5: Berman airways



Figure 9-6: ChaoAirways



Figure 9-7: Cuffed oro-pharyngeal airways

There is also a device which acts a bite blocker only (not as an airway), called **airway guard** (figure 9-8). Airway guard is designed to be attached to the breathing tube for added stability and airway protection.



Figure 9-8: Airway guard

2- Nasopharyngeal Airway:

- It is 3-4 cm longer than an oral airway. The **correct size** is assessed by approximating the diameter of the airway to **the diameter of the patient's fifth finger** (figure 9-9).
- It is **better tolerated** than the oral types in lightly anesthetized or agitated and semiconscious patients.
- It is **more traumatizing** especially in **anticoagulated patients or in children with prominent adenoids**; therefore, it should be **lubricated** and advanced in an angle perpendicular to the face. It is **contraindicated** in patients with suspected **basilar skull fractures or coagulopathies**.
- An **adjustable nasopharyngeal airway** is a modified nasopharyngeal airway with soft movable flanges. Other airways are discussed later.



Figure 9-9: Nasopharyngeal airways: The right one is with an adjustable flange.

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N.B.: Epistaxis Nasopharyngeal Airway:

It is an inflatable nasal tube, which is used to control severe hemorrhage in the nasal cavity and nasopharynx and allow bilateral stabilization of the bony cartilaginous structures after fracture of the nose. It has an anatomically contoured cuff made of silicone. The presence of silicone results in minimal adherence to the mucus membrane and a traumatic removal (figure 9-10).

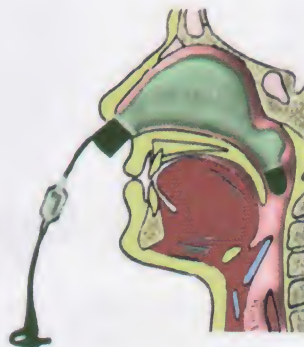


Figure 9-10: Epistaxis nasopharyngeal airway

Face Mask

Design:

There are many varieties and shapes for face masks with the following features:

- The rim of the mask is contoured and conforms to a variety of facial features allowing air-tight seal.
- Some types have **transparent bodies** which allow observation of **exhaled humidified gas**, **patient's skin color** and immediate recognition of **vomiting or regurgitation** (figure 9-11).



Figure 9-11: Varieties of face masks; disposable transparent (left), black reusable rubber (middle), and Everseal mask (right)

- The smallest size possible should be used to decrease the volume of dead space. Some pediatric masks are especially designed (with a shallow body) to decrease apparatus dead space as the **Rendell-Baker-Soucek pediatric face mask** (figure 9-12).
- **Retaining hooks** surrounding the 22-mm orifice can be attached to a head strap "**harness system**" e.g., **Clausen harness**, allowing the mask to be held in place without needing the anesthesiologist (figure 9-13).



Figure 9-12: A pediatric Rendell-Baker-Soucek mask

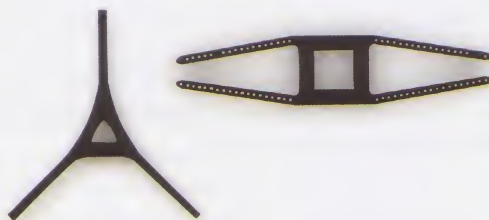


Figure 9-13: Harnesses; Clausen harness (left) and four point harness (right)

Technique:

a-One-Handed Face Mask Technique:

- The mask is held with the left hand allowing the right hand to generate positive pressure ventilation by squeezing the breathing bag.
- The mask is held against the face by the left thumb and index finger, while the middle and ring fingers grasp the mandible to extend the atlanto-occipital joint. Finger pressure should be placed on the bony mandible and not on the soft tissues supporting the base of the tongue; otherwise, the airway will be obstructed especially in pediatrics. The little finger slides under the angle of the jaw and thrusts it anteriorly.

b- Two-Handed Face Mask Technique:

- This technique is performed in difficult situations such as edentulous patients. Leaving dentures in place or packing the buccal cavity with gauze may help.
- Two hands are used to hold the mask to provide adequate jaw thrust (i.e., holding the mandible forward) and create a mask seal. Therefore, an assistant is needed to squeeze the breathing bag. In this case, the thumbs hold the mask down, while the finger tips or knuckles displace the jaw forward (figure 9-14).



Figure 9-14: Techniques of face mask application: one-handed technique (left), two handed technique (middle), and three-handed technique (right).

c- Three-Handed Face Mask Technique:

- The two hands of the anesthesiologist and one hand of the assistant hold the mask, while the other hand of the assistant is needed to squeeze the bag.
- An oropharyngeal (Guedel) airway or a nasopharyngeal airway (better tolerated) may be used to assess patency of airway, but adequate stages of anesthesia should be reached; otherwise, coughing, laryngospasm, or breath-holding may occur.

Optimal/Best Mask Ventilation Attempts should be performed before using the emergency pathway of the difficult intubation algorithm (see later) i.e., inadequate mask ventilation in patients with difficult ventilation. This is achieved by using either the 2-handed effort or 3-handed effort as above, in addition to the use of a large oropharyngeal or nasopharyngeal airway.

Risk Factors of Suspected Difficult Mask Ventilation:

- 1- Age > 55 years.
- 2- Body mass index > 26 kg/m².
- 3- History of snoring.
- 4- Edentulous patients (without teeth).
- 5- Facial hair (a beard).

Complications:

- 1- Mask ventilation **may inflate the stomach**; therefore, avoid positive pressure ventilation more than 20 cmH₂O.
- 2- Long periods of mask support **may cause pressure injury** to branches of trigeminal or facial nerves, therefore, the mask and harness or face straps' position should be changed regularly.
- 3- **Corneal abrasion and pressure on the eyes** may occur.

Nasal Mask

It may be used during dental anesthesia (figure 9-15).



Figure 9-15: A nasal black rubber mask

Laryngoscopy and Intubation

Endotracheal Tubes

Design:

- They are made of: - polyvinyl chloride (PVC) that are disposable (the most common).
or - red rubber that are reusable and autoclavable (obsolete).
- Tracheal tubes marked I.T. or Z-79 is implant-tested to ensure nontoxicity.
- A hole (**the Murphy eye**) is present to decrease the risk of complete tube occlusion.
- **The size of the endotracheal tube** is usually designated in **millimeters of internal diameter** (or less commonly in the French scale which is the external circumference of the tube in millimeters i.e., the external diameter multiplied by 22/7).
- **The length of the endotracheal tube** exceeds that required normally for oral intubation and the tube **should be cut** to the appropriate length **before use** (figure 9-16).
- Most adult endotracheal tubes have a **cuff inflation system** consisting of a valve, pilot balloon, inflating tube, and cuff. The valve prevents air loss after cuff inflation. The pilot balloon provides a gross indication of cuff inflation. The cuff creates a seal allowing positive pressure ventilation and decreases the risk of aspiration. **Uncuffed tubes** are usually used in **children** (up to 6-8 year old) to decrease the risk of pressure injury and post-intubation croup (edema). The cuff is not required because the larynx of pediatric patients is funnel shaped with the narrowest part at the cricoid cartilage (in adults, the vocal cords are the narrowest part); in addition to the loose submucosa in pediatrics which make the edema very likely to occur.
- The anesthetic circuit and the tracheal tube can be supported by a special tube support (figure 9-17).

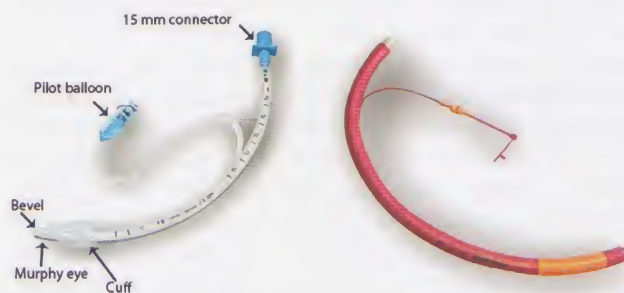


Figure 9-16: Endotracheal tubes; reusable red rubber (left) and disposable PVC tube (right)



Figure 9-17: Tube supports

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Types of Cuffs:

a- High Pressure (Low Volume) Cuff:

It is present mainly in the red rubber tubes and produces better seal, but the cuff produces **more severe ischemic damage** to the tracheal mucosa as the pressure inside the cuff exceeds that of the capillaries in the tracheal mucosa; therefore, it is less suitable for long operations or long stay in the intensive care.

b- Low Pressure (High Volume) Cuff:

It is present mainly in the disposable PVC tubes and produces more sore throat (as there is a larger mucosal contact area), and may cause aspiration, spontaneous extubation and difficult insertion (due to floppy cuff), but it produces **less severe ischemic damage** to the tracheal mucosa; therefore, it is more recommended especially for long operations or long stay in the intensive care. It is the most commonly used (figure 9-18).



Figure 9-18: Types of cuffs; high pressure low volume (left) and low pressure high volume (right)

Cuff pressure depends on:

- 1- Inflation volume.
- 2- The diameter of the cuff in relation to the trachea.
- 3- Tracheal and cuff compliance.
- 4- Intrathoracic pressure (as cuff pressure increases with coughing).
- 5- N₂O diffusion from the tracheal mucosa into the cuff which causes an increase of cuff pressure; therefore, it is recommended to readjust cuff volume after 10-15 min or fill the cuff with O₂/N₂O mixture.

Monitoring of the cuff pressure is done by a **cuff manometer (cuff pressure gauge)** (figure 9-19), but it is not reliable because the cuff pressure may fluctuate when high pressures are used to overcome poor lung compliance.



Figure 9-19: A cuff manometer and inflator

Specialized Tube Types:

1- Armored Tube: It is flexible and wire-reinforced.

Advantage: It resists kinking; therefore, it is used in head and neck surgery or in abnormal positions as prone position.

Disadvantage: It may be kinked by extreme pressure e.g., biting by an awake patient because the lumen will tend to remain occluded and the tube will need replacement. Most of the armored tubes are very malleable and need a stylet for their insertion (figure 9-20).

2- Ring-Adair-Elwyn (RAE) Preformed Tracheal Tubes (Oral and Nasal): They have been designed, in 1975, by Wallace H Ring, John C Adair, and Richard A Elwyn. They are used to direct the breathing circuit away from the field of surgery in head and neck surgery with decreasing the risk of kinking. **The RAE oral tubes** direct the breathing circuit to the feet of the patient (sometimes it is called **south-facing**) while the **RAE nasal tubes** direct the breathing circuit to the head of the patient (sometimes it is called **north-facing**) (figure 9-21).



Figure 9-20: An armored endotracheal tube with a stylet



Figure 9-21: RAE performed tubes; Oral (left), nasal (right)

3- Oxford Tube: It is L-shaped and its distal end has a fixed length (figure 9-22); therefore, it has the advantages of: - a decreased risk of bronchial intubation.

and - a decreased risk of kinking with flexed head during surgery.

4- Parker Flex-Tip Tracheal Tube. It has a soft, flexible, curved, distal tip that is designed to prevent trauma to the delicate structures of the airway. The tip, which is flanked by double Murphy eyes, flexes and yields as it is advanced into contact with protruding features of the airway anatomy (figure 9-23).



Figure 9-22: An Oxford non-kinking cuffed tracheal tube



Figure 9-23: Parker Flex-Tip Tracheal tubes

5- Laryngectomy Tube: It is used during laryngectomy as it cannot be slipped easily during the procedure, as it is curved at its distal end, unlike the REA oral tube (figure 9-24).



Figure 9-24: Laryngectomy tubes; PVC tube (left) and red rubber tube (right)

6- Micro-Laryngeal Tube: It has a small diameter to provide maximum access to the operative field although its length is comparable to a standard tube with 8 mm internal diameter (figure 9-25).



Figure 9-25: A microlaryngeal tube

7- Laser Resistant Endotracheal Tubes: They are used for laser surgery. They have two cuffs (figure 9-26). They are discussed in more details in "Chapter of Anesthesia & Otorhinolaryngologic Surgery".



Figure 9-26: Laser endotracheal tubes

8- Evac Endotracheal Tube: It has an integral suction lumen and evacuation port that provide a convenient way for continuous suctioning of the subglottic area. Continuous aspiration of the subglottic secretions helps to eliminate the source of contaminated secretions above the cuff. Therefore, this tube decreases incidence of ventilator-associated pneumonia (figure 9-27).

9- Boussionac Cardio-Pulmonary (CPR) Tube:

This tube is used during cardio-pulmonary resuscitation as there are 5 micro-capillaries moulded into the wall of the tube. When oxygen is injected through these capillaries, turbulence is created in the distal end of the tube, creating a virtual valve. Continuous insufflation of 15 liters/min of oxygen into these capillaries generates intra-pulmonary pressure of 10 cm H₂O. This is important during cardiac massage as it is not necessary to interrupt cardiac massage for performing ventilation especially if a single person is performing the resuscitation. The continuous flow of oxygen also allows satisfactory CO₂ elimination due to constant dead space washout. This also improves the quality of the alveolar air as the oxygen exits close to the carina.

There are also two capillaries for capnography and/or pressure monitoring and/or injecting medication intra-tracheally as adrenaline (figure 9-28).



Figure 9-27: An Evac Endotracheal tube



Figure 9-28: A Boussionac Cardio-pulmonary (CPR) tube

10- Electromyograph (EMG) endotracheal tube: It has two surface electrodes that allow monitoring of vocal cords and recurrent laryngeal nerve electromyography (EMG) activity during surgery (figure 9-29).

11- Cole Tracheal Tube: It is used in newborns. It has a narrow lumen at its distal portion and a wider lumen at its proximal portion to reduce air resistance to air flow, but it can injure the larynx by its narrow distal portion (figure 9-30).

12- Jackson Rees Tube: it is a pediatric tube, which is presented in different sizes 2.5-6.5 with a connector at its proximal end with an aspiration channel to allow aspiration (figure 9-31).



Figure 9-29: An EMG tube

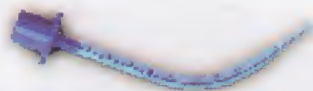


Figure 9-30: A Cole tube

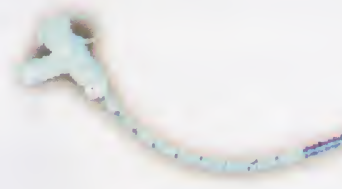


Figure 9-31: A Jackson Rees Tube

13- Double Lumen Tubes and tubes for one-lung separation: are discussed later in the chapter of "Thoracic Surgery".

14- Tracheostomy Tubes (see later).

Rigid Laryngoscopes

They are instruments used for direct examination of the larynx and intubating the trachea.

Types of Blades:

There are many types of the blades and laryngoscopes. Most of the ordinary laryngoscopes have either curved or straight blades. More recent laryngoscopes and blades are discussed later.

	Curved Blade	Straight Blade
Technique	<ul style="list-style-type: none"> - The blade is introduced to the base of epiglottis at the vallecula then it is elevated forward pressuring on the hyo-epiglottic ligament to elevate the epiglottis and expose the vocal cords. - The blade touches the upper surface of epiglottis (supplied by the glosso-pharyngeal nerve) (figure 9-32). 	<ul style="list-style-type: none"> - The blade is introduced under the lower surface of the epiglottis then it is elevated forward lifting the epiglottis to expose the vocal cord. - The blade touches the lower posterior surface of epiglottis (supplied by the vagus) (figure 9-33).
Indications	<ul style="list-style-type: none"> - In patients with small upper airway room to pass the endotracheal tube e.g., small narrow mouth, palate or oropharynx. 	<ul style="list-style-type: none"> - In patients with small mandibular space (i.e., anterior larynx), large incisors, or large infantile U-shaped floppy epiglottis. - In infants with large infantile epiglottis (figure 9-34)
Disadvantages	<ul style="list-style-type: none"> - It is useless with large floppy infantile U-shaped epiglottis. 	<ul style="list-style-type: none"> - As it touches the lower posterior surface of the epiglottis, it stimulates the vagus causing bradycardia and spasm. Therefore, anticholinergics are essential before its usage especially in pediatrics.
Examples	<ul style="list-style-type: none"> • English Machintosh blade (the most common): There are 4 sizes (figure 9-35). There is a disposable blade (figure 9-36) • American Machintosh blade (figure 9-37). • Left-handed Macintosh blade: is designed for left handed physicians (figure 9-38). • Machintosh Polio blade: is designed for patients with large breasts (figure 9-39). • Flange-less Machintosh blade (figure 9-40) is used to enhance viewing and reduce trauma. • Blechman laryngoscope blade (figure 9-41) with an angled tip is used to further elevate the epiglottis. The flange near the tip is removed to enhance viewing. • Siker Mirror American blade (figure 9-42). 	<ul style="list-style-type: none"> • American Miller blade: There are 4 sizes (figure 9-43). • English Miller blade (figure 9-44). • Wisconsin blade: There are 5 sizes (figure 9-45). • Oxford blade: There is one size only for infants (figure 9-46). • Robertshaw blade: There are 2 sizes for infants and children (figure 9-47). • Soper blade: There are 3 sizes (figure 9-48). • Seward blade: There is one size for children (figure 9-49). • Phillips blade (figure 9-50). • Snow American blade (figure 9-51) • Henderson blade: is a new blade, with an improved tip and light and with larger cross-sectional area (figure 9-52).

For more other recent devices used for intubation and ventilation see later.



Figure 9-32: A curved blade



Figure 9-33: A straight blade



Figure 9-34: Larynx of adult (left) and infant (right)



Figure 9-35: An English Macintosh blade



Figure 9-36: Disposable Macintosh and Miller blades

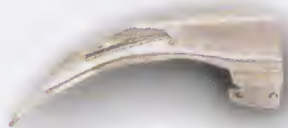


Figure 9-37: An American Macintosh blade

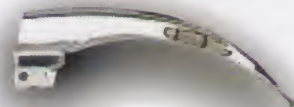


Figure 9-38: A left-handed Macintosh blade



Figure 9-39: A Macintosh polio blade and handle



Figure 9-40: Flangeless Macintosh blade



Figure 9-41: Blechman laryngoscope blade

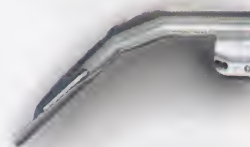


Figure 9-42: A Siker Mirror American blade



Figure 9-43: An American Miller blade



Figure 9-44: An English Miller blade



Figure 9-45: A Wisconsin blade



Figure 9-46: An Oxford blade



Figure 9-47: A Robertshaw blade



Figure 9-48: A Soper blade



Figure 9-49: A Seward blade



Figure 9-50: A Phillips blade



Figure 9-51: A Snow American blade



Figure 9-52: Henderson blades

Indications of Intubation:

- 1- Provision of a **clear airway** e.g., anticipated difficulty in using mask anesthesia in an edentulous patient or other causes of airway obstruction such as laryngeal edema or trauma.
- 2- An **unusual position** anesthesia e.g., prone or sitting.
- 3- An operative site near or involving the upper airway such as **head, neck, or thoracic surgeries**.
- 4- **Protection** of the respiratory tract **against aspiration**.
- 5- The need for **mechanical ventilation** and muscle relaxants e.g., respiratory failure.
- 6- Facilitation of **suction** from the respiratory tract.

Technique of Intubation

Preparation for Rigid Laryngoscopy:

A) Checking of Equipment:

1- The Endotracheal Tube: should be examined for the following points:

- **The size:** The proper size is chosen according to the following table, but this is only approximation; therefore, one size above and one size below should be available.

Age	Internal Diameter (mm)	Length from mid-trachea to Lips (cm)
Preterm 1 kg	2- 2.5	7
1.5 kg	3.0	7.5
2 kg	3.0	8
3 kg	3.0	9
Full-term infant	3.5	10
6-12 months	3.5	11
12-24 months	3.5	12
Child (over 2 years)	$\frac{\text{Age}}{4} + 4$ for oral intubation	$\frac{\text{Age}}{2} + 12$ for oral intubation $\frac{\text{Age}}{2} + 15$ for nasal intubation
Adult female	7.0 -8.0	19 - 21
Adult male	8.5 -9.5	21 - 22
	For all age groups, decrease 0.5 for nasal intubation.	

Tube size may also approximate to the size of the little finger or diameter of the nostril.

The correct size of the endotracheal tube can be confirmed by:

- Its easy passage into the larynx.
- Development of a **gas leak at 15-25 cm H₂O** pressure. If there is no leak, it is an oversized tube, which may cause postoperative edema especially in pediatrics. If an excessive leak occurs, it is an undersized tube, which may cause decreased ventilation and increased pollution.
- **The length:** Some anesthesiologists cut the tube to a preset length to decrease the risk of endobronchial intubation or occlusion from tube kinking.

The correct length is confirmed by:

- Advancing the tube 1-2 cm just beyond the infant's epiglottis (indicated by the black mark at the end of some tubes).
- **Auscultating** the chest until equality occurs.
- **The "1-2-3: 7-8-9" rule** is a useful guide to where the tube should be taped at the tip. The endotracheal tube of 1-kg infant should be taped 7 cm at the tip, a 2-kg infant 8 cm at the tip, and so on.
- **The cuff inflation system.** In children **below 5-6 year old, uncuffed** endotracheal tubes are usually used as cuffs may impinge on the cricoid cartilage (the narrowest part of child airway) causing postoperative edema, stridor, croup, and even airway obstruction. Also uncuffed tubes decreases the risk of accidental barotrauma.
- **The shape:** The curvature of the tube can be increased by bending the tube in a circular manner. If a stylet is used, it should be inserted into the tube, which is bent to resemble a hockey stick to facilitate intubation of an anteriorly positioned larynx (figure 9-53).
- **The patency:** The patency of the tubes especially rubber reusable tubes should be checked.



Figure 9-53: A tube is bended in a circular manner (left) and another tube is bended as a hockey stick (right)

2- The laryngoscope: should be examined for the following points:

- **The size:** Proper blade size should be chosen. In infants, Miller size 1 is used for infants > 2.5 kg while Miller size "0" is used for smaller infants.
 - **The light intensity:** is tested as it should remain constant (a blinking light indicates poor electrical contact, while fading indicates low batteries).
- Spare laryngoscope should be prepared.

- The type: either straight or curved blade.

In infants, it is better to use a **straight blade (Miller)** laryngoscope due to the large floppy U-shaped epiglottis where it is introduced until the epiglottis. The epiglottis is elevated from its under-surface by the blade, but this may cause **vagal stimulation** because the under-surface of the epiglottis is supplied by the vagus nerve (see above).

3- Suctioning unit: A proper functioning unit should be available.

B) Patient Preparation:

1- The patient's head:

- It should be at **level** with the anesthesiologist's **xiphoid process** to prevent unnecessary back strain during laryngoscopy.
- It should be in **sniffing position** (as during sniffing the morning air) because this position helps align the oral, laryngeal, and pharyngeal axes. This position is attained by **flexing the neck** at the lower cervical spines approximately 30° and **extending the head** at the atlanto-occipital joint to 20° . This position is achieved by placement of a towel or a **10-cm pillow** under the occiput, while shoulders remain on the table (figure 9-54).
- In morbidly obese patients, the sniffing position should be higher until the ear of the patients becomes in the same horizontal line with the sternum (figure 9-55).

2- Preoxygenation: with 100% O_2 by several deep breaths is done. It can be omitted in patients who refuse the face mask and who are free of pulmonary diseases.

3- Patient's eyes: should be protected by routinely taping the eye shut often after applying a petroleum-based ophthalmic ointment.

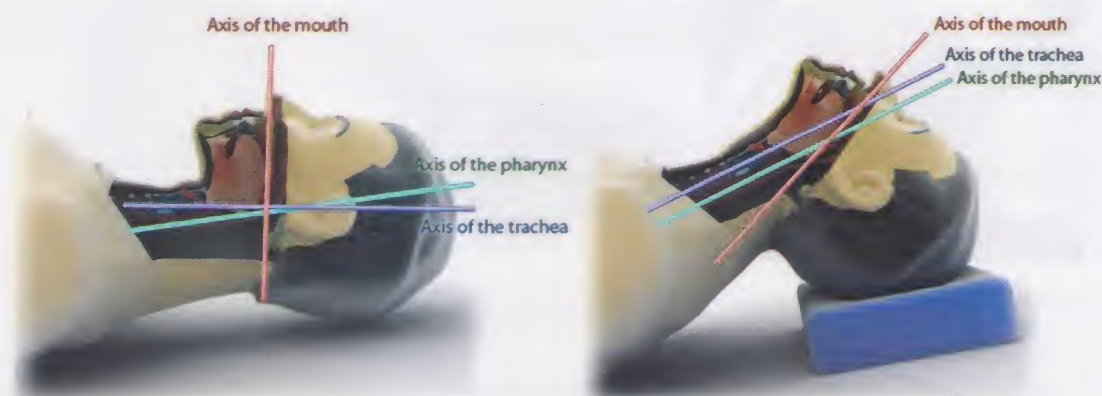


Figure 9-54: A sniffing position; the three axes (mouth, pharynx, and trachea) are not aligned without a pillow (left) and are aligned with a 10-cm pillow (right)



Figure 9-55: A morbidly obese patient with a very huge body and short neck in high sniffing position although still the external auditory meatus not reaching the level of the sternal notch

The ordinary intubation is done either through:

A) Oro-Tracheal Intubation:

- The laryngoscope is usually held in the non-dominant hand (usually the left). With the patient's mouth opened widely, the blade is introduced into the right side of the oropharynx with care to avoid the teeth.
- The tongue is swept to the left and up into the floor of the pharynx by the blade's flange.
- The tip of a curved blade is usually inserted into the vallecula, while the straight blade tip covers the epiglottis especially in children. This surface is supplied by the vagus, so vagal stimulation may occur, causing bradycardia and laryngospasm as before.
- With both curved and straight blades, the handle is raised up and away from the patient in a plane perpendicular to the patient's mandible to expose the vocal cords. Leverage of the teeth should be avoided.
- Take the endotracheal tube with the right hand and its tip is passed through the abducted vocal cords until the tube's cuff lies in the upper trachea, but beyond the larynx.
- The laryngoscope is withdrawn again with care to avoid teeth damage.
- The cuff is inflated with the least amount of air necessary to create a seal during positive pressure ventilation (feeling the pilot balloon is not a reliable method of determination of adequacy of cuff pressure). The cuff pressure should be assessed by a cuff manometer as above.
- Immediately after intubation, the chest and epigastrium are auscultated and capnographic tracing is monitored to ensure intra-tracheal location. The tube is taped to secure its position or fixed in position with a special tracheal tube restraint or holder (figure 9-56).

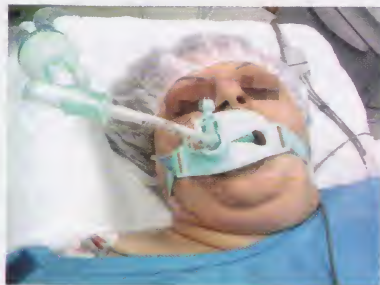


Figure 9-56: Endotracheal tube restraints or holders

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B) Naso-Tracheal Intubation:

- It is similar to oral intubation, but the tube is advanced via the nose into the oropharynx before laryngoscopy. It is **contraindicated** in patients with **fracture nose, fracture base of the skull, deviated nasal septum, or hypertrophied nasal turbinates**. The **right nostril** is usually preferred as the left facing bevel of the tube favors this side. If the right nostril is blocked e.g., deviated septum, use the left nostril.
- **Phenylephrine nasal drops** (0.5% or 0.25%) may be used as they cause vasoconstriction of vessels causing shrinkage of the mucous membrane of the nose.
- The endotracheal tube can be **lubricated** with water-soluble jelly and introduced along the floor of the nose below the inferior turbinate; at an angle perpendicular to the face till it is seen in the oropharynx where the laryngoscope is used.
- **Magill forceps** (a pediatric or an adult size) can be used to facilitate passage of the tip of the tube through the vocal cords or just head flexion can be helpful (figure 9-57).



Figure 9-57: Magill forceps

• **Packing of the throat** may be done after intubation especially for oropharyngeal operations by using a **moist cotton gauze pack**. The pack is introduced using the laryngoscope and magill forceps to be inserted on both sides of the tracheal tube in the pharynx. The pack should be applied gently to avoid abrasion of the mucosa. A **"tail" of the pack is left protruded from the mouth** to be easily remembered at the end of surgery. It is the responsibility of the anesthesiologist to remove the pack.

Optimal/Best Laryngoscopic Intubation Attempt:

Failure of one laryngoscopic intubation should force the anesthesiologist to perform the 2nd intubation in optimum conditions which include:

- 1- A reasonably **experienced** anesthesiologist should be available (the experience of using the laryngoscope is usually maximally reached after 2-3 years of experience).
- 2- No significant resistive **muscle tone** should be present (the best muscle relaxant is suxamethonium because it has a rapid onset, potent and has a short duration).
- 3- **Sniffing position** should be performed.
- 4- **Optimal external laryngeal manipulation** should be done by a **trained assistant**, instructed by the anesthesiologist. This may improve laryngoscopic grade one degree.
- 5- The length of the **blade** of the laryngoscope may be changed to a larger **size** (either Macintosh or Miller).
- 6- The **type of the blade** (sometimes) may be changed according to the patient as:
 - The Macintosh blade is preferred in patients with little upper airway room to pass the endotracheal tube e.g. small narrow mouth, palate or oropharynx.
 - The Miller blade is preferred in patients with small mandibular space (i.e., anterior larynx), large incisors, or large floppy infantile epiglottis.

Complications of laryngoscopy and Intubation

I) Errors of Endotracheal Tube Positioning:

A- Esophageal Intubation:

• No O₂ is delivered to the patient's lungs, resulting in severe hypoxia that may cause death. Therefore, if there is a doubt regarding the position of the endotracheal tube or unexplained hypoxia that occurred after intubation, removal of the tube and ventilation by mask may be life-saving.

• Esophageal intubation is detected by:

a. Reliable signs:

- 1- **Capnography** for consistent rise and fall of end-tidal CO₂ (more than 30 mm Hg for 3-5 consecutive breaths) with normal waveform is **the most reliable method**.
- 2- **Direct visualization** of the tip of the tube passing via the vocal cords.
- 3- **Fiberoptic bronchoscopy** by seeing tracheal rings and carina via the endotracheal tube.
- 4- A **Wee esophageal detector** to detect the esophagus (figure 9-58) as through which air is introduced inside the tube. If the tube lies in the trachea, the esophageal detector is re-inflated, but if the tube lies in the esophagus, the esophageal detector remains deflated because the air will not return from the stomach back to the detector.
- 5- A **colorimetric end-tidal CO₂ detector** (a disposable **chemical indicator**) to detect the expired end-tidal CO₂ (figure 9-59).
- 6- **Trans-tracheal illumination** by a special light stylet via the tube (see later).



Figure 9-58: An esophageal detector



Figure 9-59: A colorimetric end-tidal CO₂ detector

b. Unreliable signs:

- 1- Bilateral 4 quadrant **auscultation** of breath sounds with absence of gastric gurgling.
- 2- **Chest X-ray** to see the position of the tube. It is a common practice in intensive care units. The following structure can appear in chest x- film:

Structures	Radiographic levels
Anatomic structures: <ul style="list-style-type: none"> • Vocal cords • Carina 	<ul style="list-style-type: none"> - Usually over the C4-C5 or C5-C6 interspace. - Usually over the T4-T5 interspace.
Head and neck position: <ul style="list-style-type: none"> • Neutral • Flexion • Extension 	<ul style="list-style-type: none"> - Inferior border of mandible is over C5-C6 - Mandible is over T1-T2. - Mandible is above C4.
Tracheal tube position: <ul style="list-style-type: none"> • Head in neutral position • Head flexion • Head extension 	<ul style="list-style-type: none"> - Tip of the tube should be midway between the vocal cords and carina or 3-5 cm above the carina. - Tip of tube will descend 2 cm. - Tip of tube will ascend 2 cm.

3- Absence of cyanosis (hypoxia) or high pulse **oximeter** reading is unreliable, because if the patient is well preoxygenated, cyanosis (hypoxia) can be delayed up to 5 min.

4- **Expiratory condensation** of PVC tubes (breath fogging).

5- **Chest or abdominal movements** with ventilation.

6- Refilling of the anesthetic **reservoir bag**.

B- Endobronchial Intubation: (especially into the right bronchus because it forms a smaller acute angle with the trachea).

- This leads to a **large shunt** (ventilation/perfusion mismatching) which results in **hypoxia** and **decreased uptake of volatile agents**. This in turn, may lead to **barotrauma** of the ipsilateral lung and **postoperative pulmonary collapse** of the contralateral lung which later on acts as a **nidus for infection** (no change of PaCO₂ and end-tidal CO₂ slightly changes as long as the same minute ventilation is maintained). Therefore, some anesthesiologists prefer to cut the tube to an appropriate length before intubation.

- Endobronchial intubation is detected by:

1- **Unilateral breath sounds**, so auscultation should be done after securing the tube and after changing of the patient's position (neck extension or lateral rotation withdraws the tube away from the carina while neck flexion pushes the tube toward the carina).

2- **Unexpected hypoxia** with pulse oximetry. It is unreliable if the patient has inspired high O₂ concentration.

3- Inability to palpate the tube cuff in the sternal notch during cuff inflation by pressing on pilot balloon.

4- **Poor breathing bag compliance** i.e., high peak inspiratory pressure.

5- **Bronchospasm**.

C- Position of the Cuff in the Larynx: (i.e. above the cricoid cartilage).

- It causes laryngeal trauma which leads to postoperative hoarseness of voice.

- It is detected by:

1- Palpating the cuff over the thyroid cartilage.

2- Neck radiology.

II) Airway Trauma:

1- **Tooth damage:** is the most common cause of malpractice claims against anesthesiologists.

2- **Dislocated mandible:** during laryngoscopy.

3- **Lip and tongue ulcerations.**

4- **Sore throat:** occurs in 80% of patients due to trauma which results from the laryngoscope blades, airways, nasogastric tubes, endotracheal tubes especially red rubber and poorly secured tubes. They produce frictional trauma to the larynx, pharynx or tonsillar fauces.

Sore throat is increased especially if un-humidified gas is used as this causes dryness of mucous membranes.

Application of lubricants to the tube can decrease, but not prevent, the incidence of sore throat. No difference in the incidence occurs by using plain or local anesthetic jellies. Application of topical local anesthetics does not decrease the incidence of sore throat.

5- **Pressure injury of the trachea:**

- It causes **ulceration** which results in **circumferential fibrosis**. This causes **tracheal stenosis** (a late complication). Therefore, dry cough, inability to clear secretions and lastly attacks of pneumonia usually occur.

- The cause of this injury is tissue ischemia produced by prolonged intubation as the **pressure of the tube's cuff exceeds the capillary arteriolar blood pressure** (about 30 mm Hg). It is found that minimal cuff inflation just to create a seal during routine positive pressure ventilation (which is at least 20 mm Hg) can decrease tracheal blood flow by 75% at cuff contact sites; therefore, further cuff inflation or N₂O diffusion or induced hypotension can totally eliminate mucosal blood flow. Cuff pressure is measured by a cuff manometer as above.

- In patients requiring **prolonged ventilation such as in intensive care, conversion to tracheostomy** is indicated. Tracheostomy also produces more patient comfort, easier nursing care, and facilitation of suction. **The time limit** for change is debated. **Three weeks** is the empirical limit. **Recently, earlier tracheostomy** has been advocated.

6- **Edema of the glottis or trachea** especially in children at the cricoid cartilage causes post- intubation croup (see chapter of pediatric anesthesia).

7- Post-intubation **granuloma of vocal cords**:

- It is very rare, occurring in the posterior 1/3 of vocal cords especially with head and neck surgery, upper respiratory tract infection, vocal cord trauma, or high pressure of the cuff. This results in hoarseness, sore throat, dysphonia, dysphagia and sensation of foreign body in the larynx. It is treated by surgical excision by direct laryngoscopy.

8- **Vocal cord paralysis**:

- It is very rare, occurring especially with difficult intubations, obesity or long duration of intubation due to cuff pressure or trauma to recurrent laryngeal nerve. This causes hoarseness and increases the risk of aspiration.

Q: What are the causes of hoarseness after intubation?

9- **Trauma (and fracture) of cribriform plate during nasal intubation**: It may occur especially during bad technique of nasal intubation or performing nasal intubation in a patient with a fractured nose. This may lead to introduction of the tube inside the brain. Figure 9-60 shows a CT scan of a comatose child after wrong ventilation via a tube which was wrongly inserted into the brain.

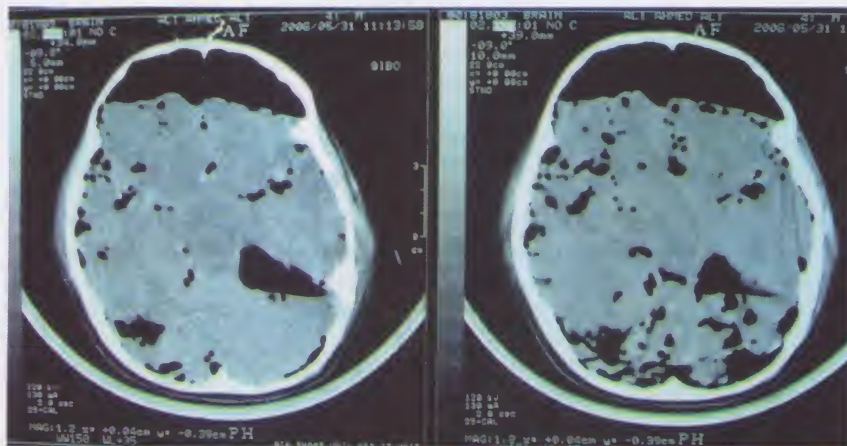


Figure 9-60: A CT brain showing pneumocephalus with air seen in the subarachnoid spaces and basal cisterns due to wrong ventilation in the brain through a previously inserted nasal tube

III) Physiological Responses to Airway Instrumentation:

I- Sympathetic Stimulation:

Effects: Sympathetic stimulation causes:

a- **Hypertension** (the blood pressure increases about 20-25 mmHg), tachycardia and arrhythmias (especially ventricular bigeminy).

b- **Increased intracranial pressure and increased intraocular pressure:**

It is avoided or decreased by:

1- Deepening anesthesia with **potent volatile agents** for 10-15 minutes (sympathetic response is blocked when a concentration equivalent to 1.5 MAC is reached).

2- **Opioids:** i.v. bolus as:

• Fentanyl	2.5-8 µg/kg	4-5 min before laryngoscopy.
• Alfentanil	15-25 µg/kg	2-3 min before laryngoscopy.
• Sufentanil	0.25-0.5 µg/kg	1 min before laryngoscopy.
• Remifentanyl	0.5-1.0 µg/kg	1 min before laryngoscopy.

- 3- **Lidocaine**: can be given by many routes: ▫ I.v. 1.5 mg/kg 2 min before laryngoscopy.
 ▫ Intra-tracheally 2 mL 2% immediately before intubation.
 ▫ Topical spray.
 ▫ Airway block.
 ▫ Jelly.
 ▫ Intra-cuff filling (it is suitable for avoiding the pressor response of extubation).

- 4- **β-blockers**: i.v. bolus as: ▫ Esmolol 0.3 - 1.5 mg/kg.
 ▫ Labetalol 10 - 50 mg.
 ▫ Propranolol 1 - 5 mg.

They are avoided in patients with history of bronchial asthma.

- 5- **Hypotensive agents**: i.v. bolus as: ▫ Na nitroprusside 1-2 µg/kg.
 ▫ Nitroglycerine.

- 6- **Ca⁺⁺ channel blockers**: i.v. as: ▫ Verapamil 0.1 mg/kg 2 min before laryngoscopy.
 ▫ Diltiazem 0.1-0.2 mg/kg 2 min before laryngoscopy.

- 7- Premedication with **clonidine** 0.2-0.3 mg.

- 8- Decrease **laryngoscopic time** ≤ 15 sec as the rise of arterial blood pressure occurs 14 seconds after the start of laryngoscopy and becomes maximal 30-45 sec after laryngoscopy.

N.B.:

- All these doses are used when a single agent is used. If a combination of agents is used, decrease the doses, otherwise severe hypotension occurs.
- All these methods can be used to decrease the pressor response of extubation, if they are given before extubation.

2- Laryngospasm

3- Post-intubation (Post-extubation) Croup

	Laryngospasm	Post-Intubation (Post-extubation) Croup
Pathology	It is a forceful, involuntary spasm of laryngeal muscles resulting in crowing inspiratory noise or absent inspiratory sounds with marked tracheal tug.	It is glottic or tracheal edema especially at the cricoid cartilage (as it is the narrowest part of the pediatric airway).
Cause and precipitating factors	Stimulation of the superior laryngeal nerve (a branch of the vagus nerve) especially: <ul style="list-style-type: none"> • patients with history of smoking, asthma, bronchitis, or chronic obstructive airway diseases. • patients anesthetized by desflurane and isoflurane (both have pungent odor). • At induction: airway, laryngoscope, or endotracheal tube. • During light anesthesia: extubation, surgical incision, anal stretch, cervical dilatation, or testicular surgeries. • At recovery: pharyngeal secretions or vomitus. N.B.: Intubation increases the incidence of bronchospasm, but has the same incidence of laryngospasm when compared with the LMA.	<ul style="list-style-type: none"> • Early childhood (1-4 years) especially in ill-patients. • Repeated intubation attempts. • Cuffed tubes or large tube sizes allowing no air leak at 15-25 cm H₂O pressure. • Prolonged surgery. • Excessive tube movement e.g. coughing, head and neck surgery. • Co-existing upper respiratory tract infection.
Time of occurrence	It is usually immediately post-extubation , but it may occur in the recovery room as the patient wakes up and chokes on pharyngeal secretions especially in pediatrics. <u>Avoided by:</u> <ol style="list-style-type: none"> 1. Extubation at awake (i.e., eye opening) or deeply anesthetized state (i.e., spontaneous breathing, but no cough). 2. Clearance of pharyngeal secretions. 3. Recovery in lateral position; therefore, oral secretions pool and drain away from the vocal cords to outside. 	Late postoperatively as it appears usually within 3 hours up to 8 hours of extubation (the time for occurrence of edema). <u>Avoided by:</u> It is better to avoid intubation in day case patients.
Treatment	1- Gentle positive pressure ventilation by a bag and mask (i.e., manually) with 100 % O₂ with application of firm digital pressure (by the middle fingers of both hands) at the laryngeal notch while doing jaw thrust and chin lift.	1- Increase FiO ₂ to 0.5-0.6, humidified 2- Drugs: <ul style="list-style-type: none"> • Dexamethasone i.v. 0.1-0.2 mg/kg • Aerosolized epinephrine via a hand-

	<p>2- I.v. lidocaine 1-1.5 mg/kg.</p> <p>3- If it persists, suxamethonium 0.25 mg/kg to paralyze laryngeal muscles and allow controlled ventilation.</p> <p>4- If it persists (hypoxia and bradycardia may occur), give atropine and 100% O₂. Re-intubation is needed.</p> <p>N.B.: Doxapram is effective for laryngeal spasm after extubation.</p>	<p>held nebulizer and mask. It is either:</p> <ul style="list-style-type: none"> - Racemic epinephrine: 0.5 mL of a 2.25% diluted in 5 mL saline). <p>Dose: 0.05 mL/Kg delivered in 10 min</p> <ul style="list-style-type: none"> - Aqueous epinephrine: (0.1% diluted in 5 mL saline). <p>Dose: 0.5 mL/Kg delivered in 10 min</p> <p>It can be repeated every 30 min if needed</p> <p>Rebound phenomenon can occur about 2 hours after cessation of therapy.</p> <p>3- If hypoxia persists;</p> <ul style="list-style-type: none"> • Re-intubate (tracheostomy may be needed). • Atropine. • 100% O₂.
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N.B.: **Application of digital pressure at the laryngeal notch:**

It is a very helpful and simple method.

Site of application:

This notch is located behind the lobule of the pinna of each ear. It is bounded anteriorly by the ascending ramus of the mandible adjacent to the condyle, posteriorly by the mastoid process of the temporal bone and cephalad by the base of the skull (figure 9-61).

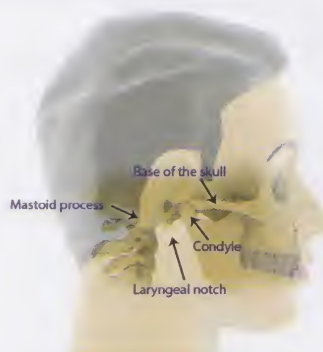


Figure 9-61: The laryngeal notch

Technique:

The therapist presses very firmly inwardly toward the base of the skull on each side using either index or middle fingers while at the same time lifting the mandible at a right angle to the plane of the body (i.e., forward displacement of the mandible or jaw thrust).

Effects:

If it is properly performed, it will convert laryngospasm within one or two breaths to laryngeal stridor, and in another breath or two to unobstructed respiration. The technique works equally well in infants, children, and adults. Besides this, the technique prevents the tongue from falling back against the posterior pharyngeal wall (if with jaw thrust).

Mechanism of action:

It is unknown, but it may be due to:

- Preventing airway obstruction by the tongue.
- The very painful stimulus that is elicited causing stimulation of several nerves including the facial nerve and the glosso-pharyngeal nerve (by pressing on the parotid gland) and vagus and perhaps sympathetic nerves.

3- Bronchospasm:

It occurs after intubation especially in:

- Asthmatic patients.
- Endobronchial intubation ± carinal stimulation.
- Over-inflated tube's cuff.
- Tube obstruction.

IV) Endotracheal Tube Malfunction:

- 1- Risk of ignition of PVC tubes in an O₂/N₂O enriched environment.
- 2- Endotracheal tube obstruction by kinking, foreign body, biting of patient, aspirations, thick pulmonary secretions, or cuff herniation (figure 9-62). Cuff herniation does not occur with current tubes.
- 3- Cuff perforation.



Figure 9-62: Cuff herniation occluding the distal end of the tube.

N.B.: **Complications Following Extubation:** 1- Airway trauma.

2- Physiological response to airway instrumentation.

Both complications may occur during extubation and they are discussed above.

Difficult Airway and Intubation

Incidence: depends on experience.

1-3: 100 of anesthetized patients have difficult intubation.

1: 1000 of anesthetized patients have failed intubation.

1: 10 000 of anesthetized patients are in the "cannot intubate, cannot ventilate" scenario.

Causes of Difficult Intubation:

I. Anesthesiologists: the most important cause.

due to 1- **Inadequate** preoperative assessment of patients.

2- **Inadequate equipment** preparation as malfunction or unavailability.

3- **Inexperience** and poor technique.

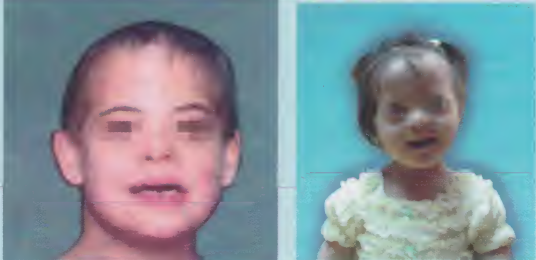

4- **Absence of a trained assistant.**

II. Patients (Preoperative Assessment)

A. Congenital Syndromes Associated with Difficult Intubation:

These syndromes have one or more anatomical features, which prevent easy intubation.

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Syndrome	Description of Difficulty	Figures
Trisomy 21 (Down syndrome) (figure 9-63)	Large tongue, small mouth, narrow nasopharynx, subglottic stenosis, short neck, irregular dentition, and atlanto-axial (cervical spine) instability. Laryngospasm is common.	 <p>Figure 9-63</p>
Goldenhar (oculo-auriculo-ventricular anomalies) (figure 9-64)	Hypoplasia of the mandible (micrognathia) and cervical spine abnormality.	 <p>Figure 9-64</p>


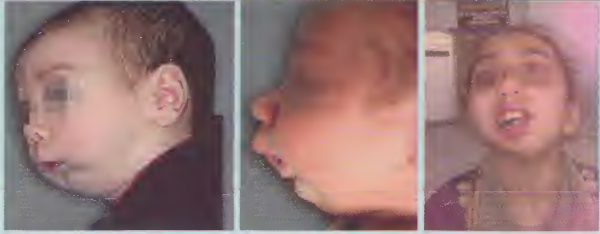




Klippel-Feil (figure 9-65)	Neck rigidity due to cervical vertebral fusion. There is also receding lower mandible, and narrow mouth opening. There is increased cardiac and genitourinary anomalies.	
Pierre-Robin (figure 9-66)	Hypoplasia of the mandible (micrognathia), posterior displacement of the chin (retrognathia), small mouth, glossoptosis, and large tongue	
Treacher Collin's (Mandibular dysostosis) (figure 9-67)	Hypoplasia of the mandible (micrognathia), molar bone hypoplasia	
Hydrocephalus (figure 9-68)	Flexion of the head and neck.	
Marfan (figure 9-69)	Long high arched palate, atlanto-axial (cervical spine) instability, and hyper-extensibility of joints causing temporo-mandibular dislocation during laryngoscopy.	
Cystic hygroma (figure 9-70)	Displacement of the trachea and larynx.	

Figure 9-65

Figure 9-66

Figure 9-67

Figure 9-68

Figure 9-69: High arched palate

Figure 9-70

B. Anatomical Features: (from above downwards examination and tests)

1- Teeth:

- **Protruding incisors (buck teeth)** as the blade enters the mouth in cephalad direction.

- **Interincisor distance** with maximal opening of the mouth: If it is **less than 3 cm** (i.e., less than 2 finger breadth), the flange of the blade cannot be easily inserted between teeth (figure 9-71).
 - **Loose teeth.**
- 2- **Palate:** Long **high arched** palate.
- 3- **Tongue:** **Large** tongue (figure 9-72).



Figure 9-71: Two patients with inter-incisor distance less than 3 cm



Figure 9-72: Two children with large tongues

4- Jaw and Mandible:

- Receding of the lower Jaw (**retrognathia**).
- Hypoplastic mandible (**micrognathia**): where the pharyngeal space becomes limited because the tongue is positioned more posteriorly. The space in which the soft tissues are going to be displaced during direct laryngoscopy is reduced.
- Obtuse mandibular angle.
- Increased anterior depth of the mandible.
- Increased posterior depth of the mandible (by x-ray) resulting in decreased jaw opening.
- Poor mandibular mobility: The patients are asked to protrude their mandible, 3 possibilities are present:
 - Class A: The lower incisors can be protruded anterior to the upper incisors.
 - Class B: The lower incisors can be brought "edge to edge" with the upper incisors.
 - Class C: The lower incisors cannot be brought "edge to edge" with the upper incisors.

Both classes B and C are associated with difficult laryngoscopy.

5- Neck:

- **Short** large muscular neck (figure 9-73).
- **Inability of the tip of the chin to touch the chest.**

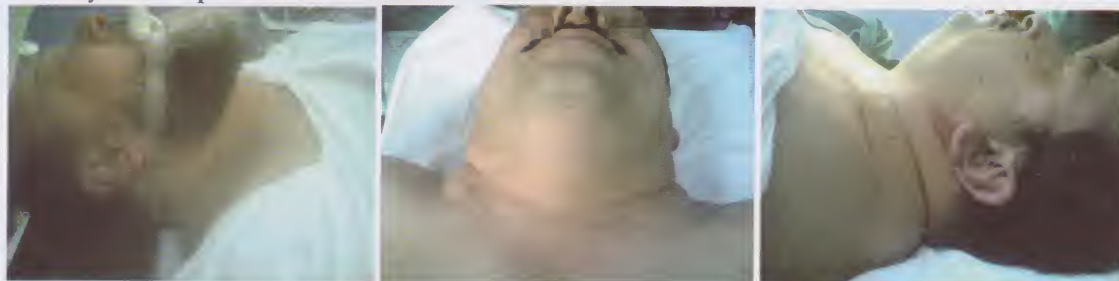


Figure 9-73: Patients with very huge necks; one of them is with a beard (difficult ventilation)

- Limitation of neck extension due to presence of soft tissues (figure 9-74).



Figure 9-74: Lipoma in the back of the neck preventing neck extension

• **Flexion/extension at the cranio-cervical junction:**

- This is best assessed by asking the patient to maximally flex his neck. The examiner's hand is then placed on the back of the patient's neck to prevent movement of the cervical spine and the patient is asked to nod (extend) his head. Difficult laryngoscopy is associated with **reduced extension of the neck**.

- Alternatively, a pen can be held against the forehead whilst maximally flexing and extending the neck. Greater than 90° of movement should be possible. Reduced movements are associated with difficult laryngoscopy.

6- **Distances:**

• Decreased distance between spine of C₁ and occiput (atlanto-occipital) causes limitation of neck extension (by x-ray).

• Decreased distance between the tip of chin and thyroid cartilage prominence (i.e., **thyro-mental distance**) **less than 6.5 cm or 3 finger breadths** with fully extended neck; this is called **Patil's test or examination** (figure 9-75).

• Decreased distance between the **tip of chin and sternum less than 12.5 cm** with fully extended head and closed mouth.

These distances indicate difficult intubation if decreased.



Figure 9-75: Thyro-mental distance less than 3 fingers

7- **Mallampati Classification:**

It is assessed by voluntary tongue protrusion with maximal mouth opening without phonating, while the patient is sitting and the head in the neutral position.

There are four classes (figure 9-76 and 9-77).

Grade	I	II	III	IV
Appearance on mouth opening (figure 9-76)				
Appearance on laryngoscopy by Cormack and Lehane (figure 9-77)				
Uvula	The entire uvula is visible.	The tip of the uvula is not visible	Only the base of uvula is visible	The entire uvula is not visible.
Larynx	Most of the glottis is visible.	Only the posterior part of the glottis is visible (arytenoids)	No part of the glottis is visible, but only the epiglottis is visible.	Not even the epiglottis is visible, only the soft palate is visible.
Degree of difficulty	No difficulty, easy intubation.	Slight difficulty, need pressure on the neck.	Severe difficulty, need stylet or bougie.	Very severe difficulty, usually with obvious pathology. It needs more complex methods e.g., fiberoptic laryngoscopy.

8- Ganzouri Airway Score:

Assessment	0 Point	1 point	2 points
Inter-incisor gap	> 4 cm	< 4 cm	Cannot open mouth
Mallampati classification	Class I	Class II	Class III and IV
Head/neck movement	> 90°	= 90°	< 90°
Buck teeth	Can prognath or edentulous	Can approximate teeth only	Cannot approximate teeth
Thyromental distance	> 6.5 cm	6.0-6.5 cm	< 6.0 cm
Body weight	< 90 kg	90-110 kg	> 110 kg
History of difficult intubation	None	Questionable	Definite
Airway score range 0-14	0	7	14

Prediction of difficult airway by scoring:

- If airway score is 0, go with normal procedures.
- If airway score is 1-2, check fibroscope.
- If airway score is 3-4, have airway management cart in the room with someone expert in using it.
- If airway score is 5 or more, awake fiberoptic intubation is strongly recommended.

Airway scores are invalid in the following conditions:

- 1- Cervical spine pathology or fracture.
- 2- Upper airway pathology such as trauma, infection, tumors...
- 3- Craniofacial anomalies such as acromegaly.

C. Acquired Causes:

1- **Decreased jaw opening** causing difficult laryngoscopy. This may be because of the following:

Muscle: reflex spasm of masseter and medial pterygoid (i.e., trismus) by infection, abscess, fracture, or tetanus.

Temporo-mandibular joint: - Fibrosis (post-infection, radiotherapy, trauma).
- Rheumatoid arthritis or ankylosing spondylitis.

Bone: - Fracture mandible or maxilla.
- Jaw wiring.

Soft tissue: tumors, edema or abscess (figure 9-78).



Figure 9-78: A patient with mandibular abscess

2- Decreased mouth opening: e.g., Xeroderma pigmentosum and burn (figure 9-79 and 9-80).



Figure 9-79: Two different cases of Xeroderma pigmentosum; the right case was previously operated upon to widen mouth opening. There is complete loss of the nose, ear, and eyes.



Figure 9-80: Patients with narrow mouth openings due to burn

3- Decreased neck movement: as in ankylosing spondylitis or burn of the neck (figure 9-81).



Figure 9-81: Patients with severe contracted necks due to burn with inaccessible jaw thrust; one of them is with bad dentition

4- Cervical spine instability or subluxation:

It is the excessive rotational or antero-posterior motion of any cervical vertebra relative to adjacent vertebrae (or the skull). Subaxial subluxation occurs when more than 2 mm loss of alignment is significant. During direct laryngoscopy, atlanto-axial instability can occur.

Causes: ▫ Degenerative diseases as rheumatoid arthritis and osteoarthritis.

▫ Congenital atlanto-axial instability as Down's syndrome, Morquio's syndrome, sporadic agenesis of the odontoid peg, Marfan's syndrome, and fetal warfarin syndrome.

▫ Trauma or fracture (figure 9-82).

▫ Tumors.

▫ Tuberculosis.



Figure 9-82: Two different plain x-rays showing normal cervical vertebrae (A) and fracture of the fifth cervical vertebra (C5) on the left and the seventh (C7) on the right (B)

Pathology:

There are 4 types of atlanto-axial subluxation (AAS):

Types	Incidence	Cause	Remarks
Anterior AAS	80%	C1 moves forward on C2 due to destruction/disruption of transverse ligament (as seen in severe rheumatoid arthritis (30%) and Down's syndrome (70%))	<ul style="list-style-type: none"> Lateral flexion radiographs show a gap of > 3 mm between the odontoid and the arch of the atlas. Atlanto-axial flexion is potentially hazardous.
Posterior AAS	Rare	C1 moves backward on C2 due to destruction of the odontoid peg itself (e.g. fracture across the base of the odontoid).	<ul style="list-style-type: none"> Lateral extension radiographs show the subluxation. Atlanto-axial extension (e.g., from direct laryngoscopy) is potentially hazardous. The odontoid process is no longer firmly held against the back of the anterior arch of C1 and on lifting the skull and C1 with a laryngoscope, the anterior atlanto-dental interval (AADI) is increased and a reciprocal decrease in the posterior atlanto-dental interval (PADI) occurs (i.e. C2 remains fixed while C1 slides anteriorly). This causes cord compression in the PADI (figure 9-83).
Vertical AAS	10-15%	Due to destruction of lateral masses of C1.	<ul style="list-style-type: none"> The odontoid pegs moves upwards through the foramen magnum to compress cervico-medullary junction.
Lateral AAS	Uncommon	Due to destruction of the C1/C2 facet joints	<ul style="list-style-type: none"> A frontal open mouth odontoid view x-ray is used. More than 2 mm difference in lateral alignment is significant.

Management:

- All patients suspected to have instability should have **lateral view X-ray neck during extension and flexion**, but this may be dangerous (as discussed above). If the **AADI** is increased to ≥ 5 mm **during flexion** (as the skull-C1 unit slides anteriorly on C2, and the anterior arch of C1 moves away from the odontoid), this is diagnostic for instability. See later for more details.

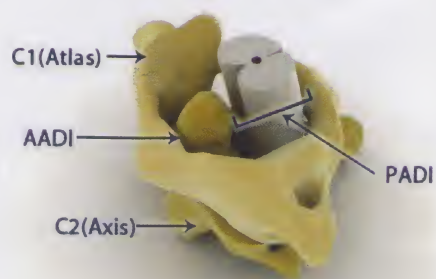


Figure 9-83: The atlas and axis

5- Airway:

- Airway edema: due to abscess (figure 9-84), infection, trauma, angioedema, or burns.
- Airway compression: due to goiter or surgical hemorrhage.
- Airway scarring: due to radiotherapy, infection, or burns.
- Airway mass: due to tumors (figure 9-85), polyps, or foreign body.
- Airway collapse: due to laryngo-tracheomalacia.



Figure 9-84: Neck abscess

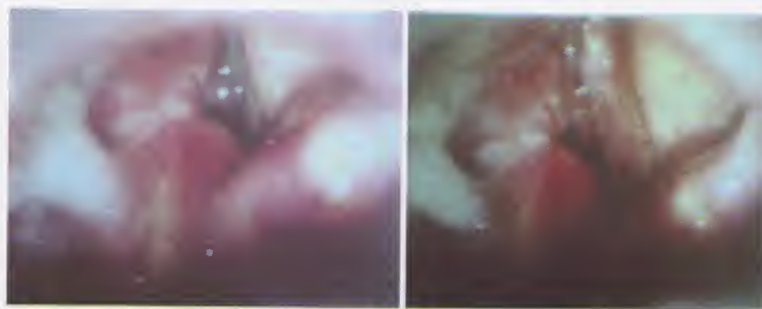


Figure 9-85: Vocal cord tumors

6- Others:

- **Morbid obesity** (figure 9-86).
- **Pregnancy.**
- **Acromegaly.**

N.B.: Previous anesthetic records should be always consulted, but a past record of normal tracheal intubation is not a guarantee for future anesthesia because acquired causes may occur leading to a change in the airway. Occasionally, patients may have a written notification of previous airway problems.



Figure 9-86: A morbidly obese female that cannot lay supine due to the buttock size. This picture was taken after she had lost 120 kg from her body weight by gastropasty surgery (notice the scar); intubation is performed in sitting position.

Preoperative (Pre-Intubation) Preparation

- 1- **Psychological** support to the patient: It makes the patient more co-operable during awake intubation. Patient consent must be taken with full **explanation** of the process and its importance.
- 2- Presence of - an **experienced anesthesiologist**,
and - a **trained assistant**.
- 3- Special "**difficult intubation**" **trolley** with a range of equipment such as different tube sizes, bougies, stylets, laryngoscopes.... etc.
- 4- Presence of a functioning **suction** unit.
- 5- Full **preoxygenation**.
- 6- Premedication.

- **Anti-sialagogues** are important especially before inhalational induction and before awake fiberoptic endoscopy because:
 - Saliva prevents action and dilutes local anesthetics.
 - Airway manipulation produces more saliva which may stimulate the airway, causing more cough, laryngospasm...etc.
 - Saliva may hinder the usage of indirect optical devices.

It is performed by glycopyrrolate (0.2-0.4 mg), 15-60 min before intubation, preferred (to atropine) as it does not cross the blood brain barrier; therefore, it has no effect on consciousness.

- **Sedatives**: are given in small doses or omitted to avoid decreased level of consciousness. They are absolutely contraindicated in patients with upper airway obstruction.

Techniques for Difficult Intubation:

There are many methods of **trans-laryngeal intubation**. The choice between them depends on:

- experience of the anesthesiologist,
- availability of the technique, and
- patient's condition e.g., no nasal intubation in face trauma.

These techniques include:

- An awake or asleep patients.
- An oral or nasal route.
- A blind, laryngoscopic, or fiberoptic methods. There are different types of laryngoscopes and fiberoptic devices.

These provide about 12 different methods e.g., awake nasal fiberoptic intubation. In addition to:

13. Laryngeal mask (used as a stylet through which a smaller tube or a bronchoscope can pass).

14. Combi-tube.
 15. Retrograde intubation
 16. Tracheostomy or cricothyrotomy (surgical airway).
- Other methods of ventilation include:
17. Mask ventilation.
 18. Nasopharyngeal airway or cuffed oropharyngeal airway (COPA).
 19. Jet ventilation.

The American Society of Anesthesiologists' Difficult Airway Algorithm (**ASA-DAA**) should be followed on facing a case of a difficult intubation. The following considerations should be noticed before using the algorithm:

1- Obviously, **prediction of difficult airway or intubation is much safer** than facing a problem of failed intubation drill. When facing this problem, **early decision to use** the algorithm of difficult airway and intubation is much safer.

2- Before using the ASA-DAA, consider the relative merits and feasibility of basic management choices between:

- Non-surgical or surgical techniques for initial approach to intubation.
- Awake or asleep intubation.
- Preservation of spontaneous ventilation or the need of muscle relaxation.

3- **The Airway Approach Algorithm (AAA)** (figure 9-87) is an algorithm to help in decision making either choose awake intubation or intubation after induction of general anesthesia. In other words; it helps guide entrance into the ASA-DAA (figure 9-88). It is the root of the ASA-DAA. The clinician must apply **his or her own experience and judgment** on moving through the AAA. There are no absolute answers. "AAA" consists of 5 questions:

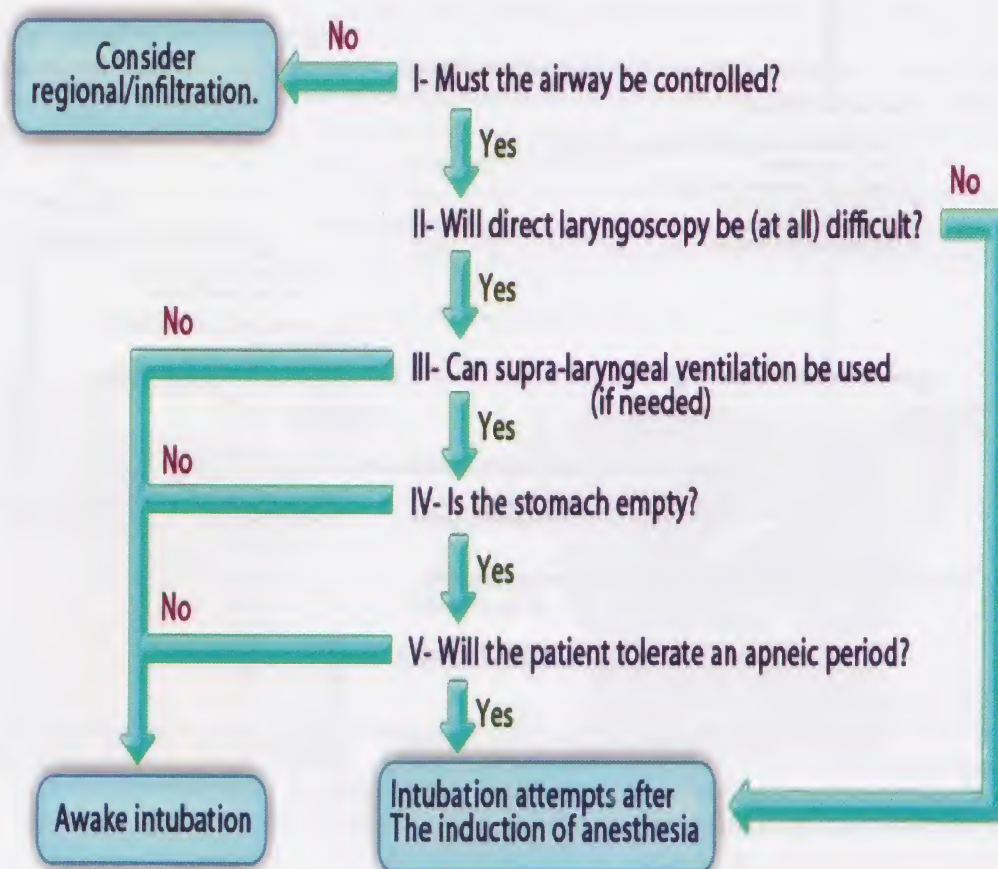
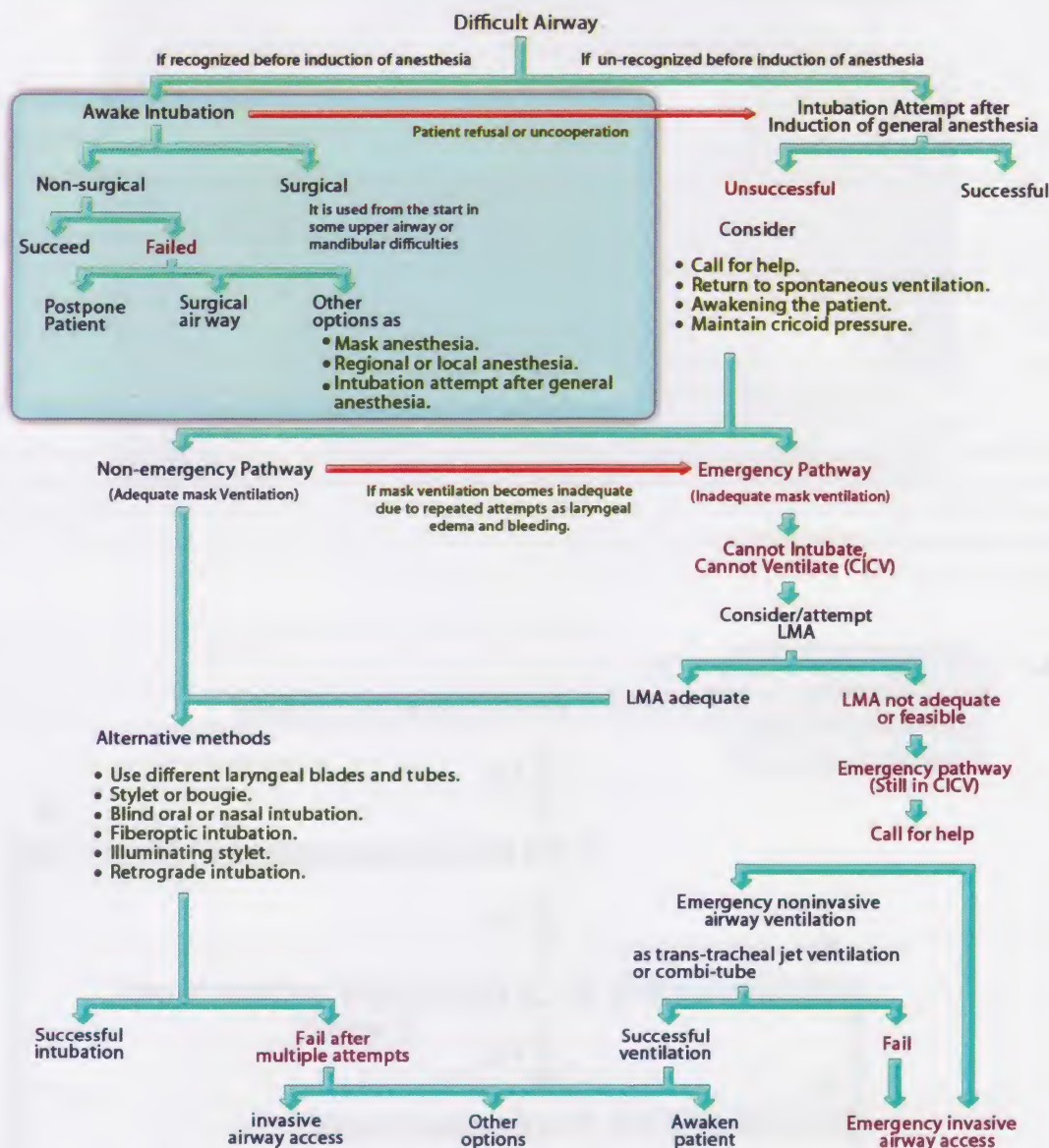


Figure 9-87: The Airway Approach Algorithm

The American Society of Anesthesiologists' Difficult Airway Algorithm (ASA-DAA)



Confirm tracheal intubation or LMA placement with exhaled CO₂.

Figure 9-88: The ASA-DAA

Awake Intubation

It can be done by either: direct laryngoscopy, blind intubation (oral or nasal), fiberoptic intubation, or by an illuminating stylet.

The choice depends on the anesthesiologist's training and experience.

Awake intubation is done in the following steps:

1- Patient Preparation: (as above)

- **Explanation, Psychological Support, and Patient's Consent:** Patient understands safety to gain patient's cooperation.

- **Desiccation:** i.e., dryness of the airway by an anti-sialagogue (e.g., glycopyrrolate 0.2-0.4 mg i.v. 15 min before starting).
- **Sedation:** is essential in proper doses which maintain patient airway control.

2- Preparation of the Nose (Dilatation):

It should be done **in all patients**, regardless either **nasal or oral intubation** is intended, unless a medical contraindication is present. If oral intubation is found difficult, nasal preparation is now a good choice.

Method: by a **vasoconstrictor** to decongest and shrink the nasal mucosa which widens the space and reduces the risk of bleeding during manipulation e.g., oxymetazoline (*Afrin*), or phenylephrine nasal drops, or 40% cocaine spray (a local anesthetic and decongestant).

3- Anesthesia of the Airway:

A) For Nasal Intubation:

Anesthesia of the Nasal Passage and Nasopharynx:

- This area is innervated by the anterior ethmoid nerve (anterior 1/3) and nasopalatine nerve.
- **Cotton swabs (or cotton tipped applicators)** soaked with **local anesthetic** (4% lidocaine solution or 5% lidocaine ointment) are advanced slowly into the nasal passage, first up towards the cribriform plate, and then directly posterior until the bony feel of the sphenoid bone is encountered. The swabs are advanced slowly and incrementally until the patient winces or otherwise exhibits discomfort (i.e., push to pain). This may take up to 5 minutes to accomplish. **Lidocaine spray** can be used **instead**.
- Then, a **well lubricated soft nasopharyngeal airway** (size 6 or 7) is then gently inserted into the nasopharynx and left in situ for 3-5 min. then removed to apply the lubricated tube or fiberoptic shaft. Lidocaine spray is introduced through the nasopharyngeal airway to anesthetize the oropharynx and supra-glottic area.
- Then anesthesia of the hypopharynx, larynx, and trachea is performed.

B) For Oral Intubation:

Anesthesia of the posterior 1/3 of the tongue and posterior oropharyngeal wall (gag reflex): There are two methods:

- **Without a needle** (easier): by applying a **new lidocaine soaked swab** (or lidocaine spray) along the tongue until it **contacts the base of the palato-glossal arch** (an arch which travels from the uvula to the base of the tongue). A few moments later, the swab can generally be re-advanced. The patients can close their mouths on the swabs and hold them in position for 5 minutes.
- **With a needle:** bilateral injection of 2 mL of local anesthetic into the **base of the anterior tonsillar pillars (palato-glossal arch)**, while the tongue is laterally retracted by a tongue blade. Injection is done by 25-gauge spinal needle (it blocks the lingual and some pharyngeal branches of the glosso-pharyngeal nerve) (figure 9-89).
- Then anesthesia of the hypopharynx, larynx, and trachea is performed.

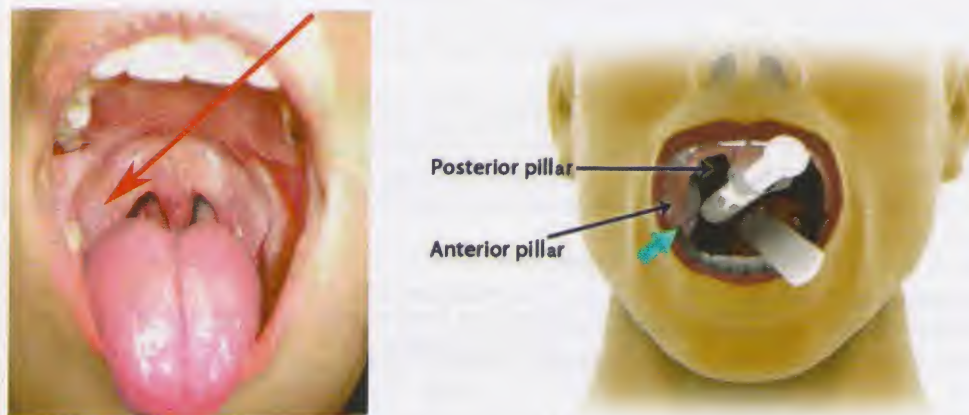


Figure 9-89: Anesthesia of the posterior 1/3 of the tongue and oropharynx at the inferior portion of the anterior tonsillar pillar (palato-glossal arch) indicated by the arrow

C) Anesthesia of the Hypopharynx, Larynx and Trachea: (for both oral and nasal routes)

1- Bilateral Superior Laryngeal Nerve Block: (for oral and nasal routes)

It is used to anesthetize airway above the glottis.

The hyoid bone is located, and 3 mL of 2 % lidocaine are infiltrated 1 cm below each greater cornu where the internal branch of the superior laryngeal nerve penetrates the thyrohyoid membrane (figure 9-90).

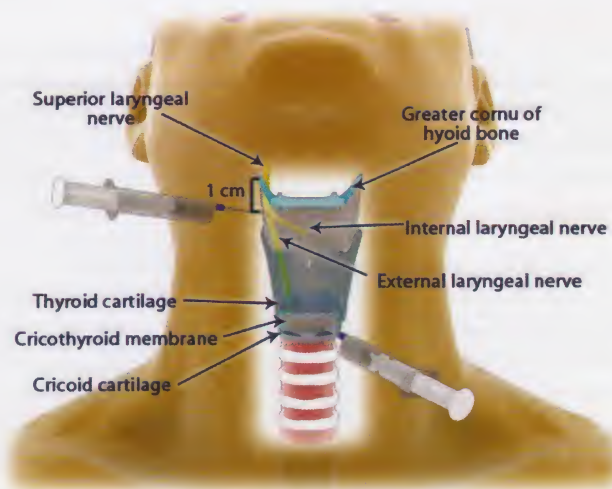


Figure 9-90: Bilateral superior laryngeal nerve block and trans-tracheal block

2- A Trans-Tracheal Block: (for oral and nasal routes)

After extending the neck, the cricothyroid membrane is located and after confirmation of an intra-tracheal position by aspiration of air using a 21-G needle in the midline, 4 mL of 4% **lidocaine are injected inside the tracheal lumen** at the end of expiration. This causes deep inhalation and coughing immediately after injection. This deep inhalation and coughing distribute the lidocaine throughout the trachea.

N.B.:

- Anesthesia of the hypopharynx, larynx, and trachea depress protective cough reflexes and swallowing reflex. This increases the risk of aspiration although the patient is fully awake.
- A trans-tracheal block alone causes transient obstruction of the pharynx due to loss of reflex regulation of the airway caliber at the level of the glottis.

Alternative Techniques for Anesthesia of the Hypopharynx, Larynx, and Trachea:

Either technique can be used instead of the needle injection methods. They are needless techniques.

1- Spray as You Go Technique:

- It is done in patients who are at risk of aspiration. Instead needle anesthesia, injection aliquots of lidocaine via the suction port of the fiberoptic laryngoscope as it is advanced, is performed.
- The calculated maximum safe dose of local anesthetics should not be exceeded.

2- Dripping Technique:

- A 10 cc syringe fitted with a large plastic catheter is filled with lidocaine (2%). The patient **extends the tongue maximally**, and the anesthesiologist takes unfolded gauze, wraps the tip of the tongue, and does not allow the patient to retract the tongue.
- After the patient is assured that there is no needle, the catheter is inserted over the tongue until the distal tip is at the oropharyngeal junction.
- **Lidocaine is dripped slowly onto the tongue base.** The procedure may take up to 1-2 minutes and all 10 cc of lidocaine need not be used. At first, the patient will cough. Once the coughing subsides, the gurgling of the lidocaine deep in the airway can be heard.
- **Holding the tongue** in this manner prevents the patient from swallowing the lidocaine, and encourages its aspiration.

Role of Regional Anesthesia in a Difficult Airway Patient:

As there is a risk of failure or complication from regional anesthesia which needs to control airway, **do not depend only on the regional anesthesia in difficult airway** because it does not solve the problem; therefore, you must have the ability to either:

- Stop the surgery, if it is very small and superficial.
- Change to a new plan of airway control in cases of regional anesthesia failure or complication.

Extubation

It is a very important as morbidity and mortality can still occur during the period of extubation.

Criteria for Extubation:

A- Global Criteria: include:

- Return of consciousness as - ability to follow commands e.g., opening the eyes.
- Bispectral monitor is 90-100.
- Return of ability to protect the airway.
- Adequate reversal of residual neuromuscular blockade by clinical tests and nerve stimulators.
- Absence of hypothermia.
- Presence of normal metabolic milieu (e.g., no significant anemia, acidosis, or electrolyte abnormality).
- Stable hemodynamic status.

B- Respiratory Criteria: include:

- Spontaneous breathing.
- Regular respiratory rate and less than 30 breath/min.
- Adequate tidal volume > 5 mL/kg.
- Adequate vital capacity > 10-15 mL/kg.
- Negative inspiratory force (and airway pressure) less than -20 to -30 cm H₂O.
- Arterial blood gases on FiO₂ less than 0.4 are:

- pH	7.35-7.45
- PaO ₂	> 60-80 mm Hg.
- SpO ₂	> 90 %
- PaCO ₂	< 50 mm Hg

For more details, see the weaning in the chapter of "Intensive (Critical) Care".

Technique of Extubation:

1- Patient's Position:

- It is preferable to put the patient in lateral position during extubation especially if there is a risk of aspiration.

2- Suctioning the Pharynx before Extubation:

- Oropharyngeal suctioning is done from the most dependent part, but it is best performed under vision to avoid trauma to pharyngeal mucosa, uvula or epiglottis.
- It decreases the risk of aspiration and laryngeal spasm.
- **Tracheobronchial suctioning** may be done by **soft sterile** suctioning catheter with a diameter **less than half the internal diameter of the tube**. The catheter is occluded during insertion and suction is applied during withdrawal.
- Then the tube is untapped and the cuff is deflated completely just before extubation.

3- Time of Extubation:

- It is part of the art of anesthesia that develops with experience.
- Generally,
 - Adequate recovery from muscle relaxant should be established before extubation.
 - Extubation is done during either deep anesthesia or totally awake condition (**it must be avoided during light plane of anesthesia i.e., between deep and awake states, as during light anesthesia there is increased sensitivity of reflexes which increases the risk of laryngospasm**) (figure 9-91).

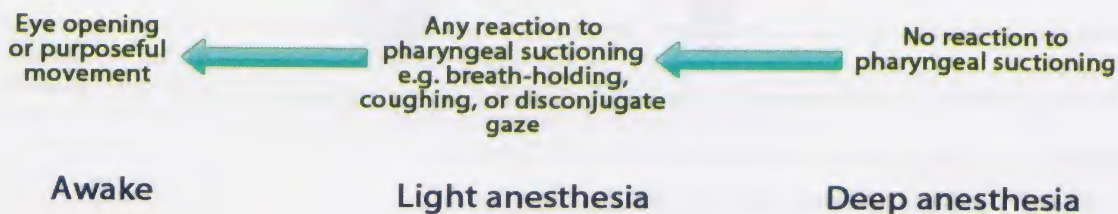


Figure 9-91: Stages of recovery

4- Types of Extubation:

a- Awake Extubation:

- It is done when the patient is fully awake.
- Indications:
 - Generally, **all anesthetized** patients should be extubated awake.
 - Patients at risk of aspiration i.e., with **full stomach** (empty the stomach with an orogastric tube while the patient is still paralyzed).
 - Patient's with airways which may be **difficult to control after endotracheal tube removal**.
- Effects: coughing (bucking) on endotracheal tube causes sympathetic stimulation (i.e., **pressor response**) which:
 - Increases heart rate, blood pressure, intracranial tension, and intraocular pressure which in turn increases bleeding.
 - Induces bronchospasm in asthmatic patients.
 - Causes wound dehiscence.
- **To decrease the pressor response of extubation**, the same pretreatment is done as with intubation (see above).

b- Deep (Smooth) Extubation:

- It is done while the patient is **deeply anesthetized** by increasing the depth of anesthesia or giving **opioids, or 10-20 mg propofol**. This is accompanied by measures to **decrease the pressor response of intubation** (as above). Removal of the endotracheal tube is only done after fulfilling the criteria for extubation.
- Indications: mainly **to avoid the pressor response of extubation** in patients who can not tolerate it e.g., asthmatic, hypertensive, ischemic, ophthalmic or neurosurgical patientsetc, but deep extubation is contraindicated in patients with risk of aspiration or expected difficult control of airway e.g., those with airway edema or difficult mask ventilation. Therefore, if both awake and deep extubation indications are present, **awake extubation indications have the priority**.

5- Withdrawal of the Endotracheal Tube:

- It is done in a single smooth motion along its curve axis as careless withdrawal in straight line may damage laryngeal structure.
- Extubation is preferred **during inspiration** when larynx is dilated. Some anesthesiologists generate a positive pressure in the trachea during withdrawal by squeezing the bag to propel secretions from the trachea into the pharynx.
- Sometimes, patients bite on the endotracheal tube (especially in case of absence of oropharyngeal airway and in agitated patients); therefore, an **oral appliance** as **Abelson Jaw Spreader** can be applied and rotated smoothly to open the jaw and prevent biting on the tube. It can also be used in traumatized patients or those with convulsions when they have trismus or clench their jaw. **Oberto mouth prop** is another device that can be used in electro-convulsive therapy and epileptic spasm. It contains **central air vent** (figure 9-92).

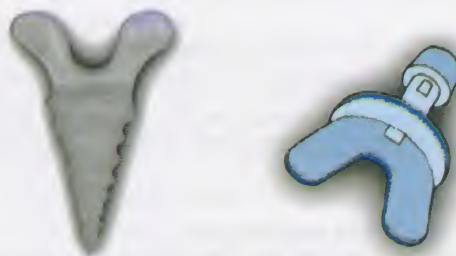


Figure 9-92: An oral appliance; Abelson Jaw Spreader (left) and Oberto mouth prop (right)

6- After Extubation:

- Ventilate by 100% O₂ by face mask ± airway to:
 - avoid diffusion hypoxia of N₂O.
 - provide a pulmonary reservoir of O₂ in case of breath-holding or coughing.
- Put the patient in lateral recovery position to:
 - avoid risk of aspiration.

- detect possible bleeding e.g., after tonsillectomy (tonsillectomy position).
- Assess the patient as regards:
 - ability to maintain airway.
 - ability to cough.
 - presence of secretions.

Difficult (Special) Extubation:

Failure to fulfill the criteria of extubation (see above) is considered a case of difficult extubation. There are special conditions such as:

1- Tracheomalacia:

- If it is suspected, **direct visualization** of airway patency is suggested. The **fiberoptic bronchoscope** can be used to assess airway collapse and vocal cord movement as the endotracheal tube and bronchoscope together are slowly pulled back. If tracheal collapse is noted, the tube and bronchoscope should be immediately re-advanced.

2- Laryngeal Edema:

- It can occur due to airway trauma or even after repeated attempts of intubation in patients with difficult intubation.
- It can be assessed by:
 - Inspection: presence of external neck edema, venous congestion, duskiness of the head and neck, edematous tongue that extends beyond the incisors, and conjunctival and lid edema suggest laryngeal edema.
 - Absence of air leak around the deflated cuff indicates laryngeal edema.
 - Bronchoscope.
 - Airway trauma history.
- **Extubation trial is done** as follows:
 - At first, **topical anesthesia is applied** to the airway before examination to limit the stimulation that may result from examination, extubation, and possible re-intubation of the airway.
 - A **ventilating tube exchanger, a jet stylet (Cook airway exchange catheter) or fiberoptic bronchoscope shaft** may be placed via the endotracheal tube, so when the tube is removed, it can immediately be replaced.
 - Consider a tongue stitch to pull the tongue forward if obstruction with the tongue is likely to be a problem.
 - The **airway is observed** for as long as **one hour** after extubation.
 - **Auscultation** of the larynx must be performed frequently **looking for stridor**.
 - Continuous **pulse oximetry** is mandatory.
- Have a back up plan as laryngeal mask airway, combitube, or crico-thyroidotomy.

N.B.: The Cuff Leak Test:

The test can be performed either on a spontaneously breathing or mechanically ventilated patient:

a- On a spontaneously breathing patient: The endotracheal tube cuff is deflated and the opening of the endotracheal tube is blocked, then listening to a leak around the cuff while the patient inspires is performed.

b- On a mechanically ventilated patient (assist/control mode):

- An inspiratory tidal volume and 6 subsequent expiratory tidal volumes are recorded after oropharyngeal suctioning, and endotracheal cuff deflation. Six cycles are recorded because it has been found that the exhaled tidal volume values have decreased decrementally during the first few breaths before reaching a plateau.
- The **leak** is measured as the **difference between the preset inspiratory tidal volume and the average of the lowest 3 of the subsequent 6 expiratory tidal values**.
- A leak of **less than 110 mL** is considered a **positive result** of the cuff leak test and indicates that the patient is at risk for post-extubation stridor secondary to laryngeal edema.
- Disadvantage of the test: The test has **poor sensitivity** in detecting post-extubation stridor and has **low positive predictive value**.

3- Hemophilic Patients:

Gentle oral suctioning under direct vision is appropriate to remove all secretions because suctioning of the oropharynx of hemophilic patients can trap mucosa in the suction catheter and result in the formation of an oral hematoma.

4- Accidental Extubation:

It should not be allowed during surgery especially in abnormal positions e.g., prone or sitting position.

5- Extubation of Obstructed Sleep Apnea Patients:

- **Awake extubation** is essential either in the operating room or the **tube is left** in situ to be removed later, after a period of postoperative mechanical ventilation.
- **Airway obstruction** after extubation is very **common** in obstructive sleep apnea patients **especially** those with oral or nasal surgery; therefore, **nasal packing**; if needed, should be around the nasopharyngeal airway (creating a central conduit for gas exchange); otherwise,
 - negative pressure pulmonary edema
 - and - death from asphyxia may occur.
- **Extubation** is done in the **semi-upright position** to decrease compression of the diaphragm by abdominal contents.
- An **oro-pharyngeal and/or a long naso-pharyngeal airway** should be in-situ and **2- or 3- handed ventilation** should be available.
- The endotracheal tube should be removed over an **airway exchange catheter or fiberoptic bronchoscope** if the possibility of re-intubation is suspected and the patient had difficult intubation on induction.
- If the patient was on continuous positive airway pressure (**CPAP**) mode, either nasal or full face mask[†], preoperatively, the patient should be on CPAP postoperatively.

Other conditions related to extubation include:

- **Indications of Awake and Deep Extubation:** see before.
- **Complications of Extubation:** see above.

N.B.: Difficult weaning from mechanical ventilation is a condition that differs from difficult extubation.

Management of the Obstructed Airway

Causes of Obstructed Airway:

A) **Upper Airway Obstruction Causes:** They are either:

- **Supra-glottic causes (Oropharyngeal):** such as trauma, tumor, or infection.
- **Glottic causes (laryngeal causes):** lesions in and around the larynx; usually malignant or infective.

B) **Lower Airway (Subglottic) Obstruction Causes:**

- **Mid-tracheal causes:** They cause obstruction at the mid-trachea. This is usually secondary to retrosternal goiters.
- **Lower tracheal and bronchial causes:** They are usually large mediastinal masses e.g., lymphomas, thymomas, and carcinomas.

Patient Assessment:

A careful history, examination, and investigations should be done to assess the **level, cause, and degree** of the airway obstruction.

a- **Partial Obstruction of the Airway:**

- **Noisy, stertorous breathing** (as the air stream becomes turbulent when it traverses narrowed passages).
- The patient is usually **anxious, diaphoretic**, with circumoral pallor or cyanosis.
- **Active accessory muscles of respiration.**
- The patient may assume **unusual positions to facilitate breathing** e.g., patients may sit up and lean forward to have gravity assist in keeping a disrupted tongue and mandible from falling backward and impacting into the upper airway and closing it completely.
- Abundant **secretions or blood** and damage to the face may be present.
- **Paradoxical respiration:** in which the thoracic cage and abdominal movements will be in the opposite direction i.e., inflation on expiration and deflation on inspiration due to forceful contraction of the diaphragm in an attempt to draw air past the obstruction. This leads to negative intra-thoracic pressure during inspiration which will suck in the thorax (**Rocking boat pattern of respiration**).
- Partial airway obstruction may be:
 - **Mild:** Airway obstruction and stridor occur **with severe exercise**.
 - **Moderate:** Airway obstruction and stridor occur with lying in **supine position**.
 - **Severe:** Airway obstruction and stridor occur at **rest** or with **sitting position**. It indicates a reduction of airway diameter of at least 50%. There may be a history of waking up at night in panic and sleeping upright in chair.

b- Complete Obstruction of the Airway:

- **Silent** as no air is moving i.e., no turbulence.
- Patients will **struggle against their closed airway**.
- **Paradoxical respiration (Rocking boat)**.
- **Death** occurs by asphyxia **within 3-5 minutes** unless urgent cricothyrotomy is performed.

Airway Management and Induction of General Anesthesia**A) Upper Airway Obstruction:**

Management is determined according to the degree of expected difficulty and airway obstruction:

1- Cases with Little Expected Difficulty and no Airway Obstruction:

- **I.v. induction** (especially with patients at **risk of aspiration**).
- **Inhalational induction** (especially with patients **not at risk of aspiration**).

2- Cases with Severe Expected Difficulty and Little Airway Obstruction:

- Use **inhalational induction only** (i.v. induction is an absolute contraindication) because during inhalational induction, airway obstruction may increase causing limitation of the uptake of inhalational agent. This causes awakening of the patient which in turn protects his airway.
- **An otorhinolaryngeal surgeon** should be **ready with a tracheostomy tray** and a rigid ventilating bronchoscope close to hand.

3- Cases with Severe Airway Obstruction:

- **Awake intubation** is used.
- **An otorhinolaryngeal surgeon** should be **ready with a tracheostomy tray** and a rigid ventilating bronchoscope close to hand.

4- The Most Severe Cases of Airway Obstruction:

- **Surgical access i.e., tracheostomy** under local anesthesia from the start.
- **Helium** may help ameliorate stridor whilst the tracheostomy is performed. Heliox (premixed helium/oxygen) contains only 21% oxygen. The oxygen content may be increased by adapting rotameters to fit the Heliox cylinder, or using a simple "Y" connector and an oxygen cylinder.

B) Mid-Tracheal Obstruction:

As the usual cause is a retrosternal goiter, assessment of airway obstruction should be done by **CT scan and MRI**.

1- Cases with Easy Intubation: (They are the most common)

- **Conventional intubation techniques** and induction of general anesthesia can be performed.

2- Cases with Difficult Intubation and Airway Obstruction:

- **Awake fiberoptic intubation** in cooperative patients.
- **Inhalational induction** in uncooperative patients

A very small tracheal tube should be used to bypass the obstruction.

N.B.: **An emergency tracheostomy** may **not** be an **option** since access to the trachea may be compromised and difficult by the presence of a large neck mass. In some patients, it may be possible to perform a tracheostomy, but the tube may not be long enough to bypass the obstruction.

C) Lower Tracheal and Bronchial Obstruction:

They are very difficult cases. Sudden respiratory obstruction can occur at any stage of the anesthesia. They are best managed by:

- Undergoing surgery with **local infiltration** (the best if possible).
- The use of a **rigid intubating bronchoscope** to relieve the obstruction (may be lifesaving).
- Transfer to a unit where facilities for **extracorporeal oxygenation** are available (may be necessary in some cases).

In Patients with Glottic or Subglottic Obstruction of the Airway:

Airway management can be performed by:

- 1- Endotracheal tubes.
- 2- Trans-tracheal jet ventilation.
- 3- Surgical airways such as cricothyrotomy.

All supra-glottic (supra-laryngeal) ventilatory devices such as laryngeal mask airway, combi-tube...etc cannot be used as they cannot supply air to the trachea to bypass the obstruction.

Recent Airway Devices and Techniques

They include:

A) Endotracheal Tube Guides:

a- Stylets:

- | | |
|---------------------------|----------------------|
| 1- Tube Stylet. | 2- Schroeder Stylet. |
| 3- Parker Flex-it Stylet. | 4- Radlyn Stylet. |

b- Tube Introducers and Exchangers:

- | | |
|---|---|
| 5- Eschmann Tracheal Introducer (Gum Elastic Bougie). | 6- Frova Intubating Introducer. |
| 7- Arndt Airway Exchange Catheter Set. | 8- Aintree Airway Exchange Catheter. |
| 9- Cook Airway Exchange Catheter. | 10- Patil Two-Part Intubation Catheter. |
| 11- Musa Muallem Tube Introducer. | 12- Rivier Introducer Airway. |
| 13- Mizus Endotracheal Tube Replacement Obturator (METTRO). | |

c- Tube Introducers and Airways:

- | | |
|---|------------------------|
| 14- Cord Care™, Intubating Sheath. | 15- Augustine Guide. |
| 16- Intubating Berman Guide. | 17- Ovassapian Airway. |
| 18- Williams Airway Intubator. | |
| 19- Supraglottic Airway Laryngopharyngeal Tube (SALT) | |

B) Lighted Stylets:

- | | |
|---------------------------------------|---|
| 1- Trachlight (Lightwands). | 2- Seeing Optical Stylet (SOS). |
| 3- Flexible Airway Scope Tool (FAST). | 4- Bonfils Retro-molar Intubation Fiberscope (Levitan). |

C) Rigid Laryngoscopes:

- | | |
|---|--|
| 1- Flexible Tip or Levering McCoy Laryngoscope (Flipper) (Heine Blade). | |
| 2- Flexiblade Laryngoscope. | 3- Dörge's Emergency Laryngoscope Blade. |
| 4- Patil-Syracuse Handle. | 5- Magboul Laryngoscope. |
| 6- IntuBrite Laryngoscope | 7- Viewmax Laryngoscope or Truview. |
| 8- Trachview Videoscope. | 9- GlideScope. |
| 10- Macintosh Video Laryngoscope and X-lite Video Set. | |
| 11- McGrath Series 5 Fully Portable Video Laryngoscope. | 12- Pentax Laryngoscope. |
| 13- AirTraq Laryngoscope. | 14- Res-Q-Scope. |

D) Indirect Rigid Fiberoptic Laryngoscopes:

- | | |
|--------------------------------|-----------------|
| 1- Bullard Elite Laryngoscope. | 2- UpsherScope. |
| 3- Wu Laryngoscope (WuScope). | |

E) Supra-Glottic (Supra-laryngeal) Ventilatory Devices:

These devices are sometimes called **intermediate airways**.

- | | |
|--|---------------------------------------|
| 1- Laryngeal Mask Airway (LMA). | 2- Air-Q masked laryngeal airway |
| 3- Esophageal-Tracheal Combi-Tube. | |
| 4- Pharyngeal-Tracheal Lumen Airway (PTL Airway). | 5- Laryngeal Tube. |
| 6- Esophageal Obturator Airway. | 7- Esophageal Gastric Tube Airway. |
| 8- Pharyngeal Airway X-press (PAX). | 9- Cobra PLA (Peri-Laryngeal Airway). |
| 10- Cuffed Oro-Pharyngeal Airway (COPA). | |
| 11- Glottic Aperture Seal Airway (Soft Seal) (Vital Seal). | |
| 12- Streamlined Pharynx Airway Liner (SLIPA). | 13- i-GEL Airway. |
| 14- Cuffed Pharyngeal Tube. | |

Other supra-glottic devices:

- Face and Nasal Mask Ventilation.	- Naso- and Oro-Pharyngeal Airways.
- Augustine Guide.	- Intubating Berman Guide.
- Ovassapian Airway.	- Williams Airway Intubator.

F) Special Airway Techniques:

- | | |
|--|--|
| 1- Flexible Fiberoptic Intubation. | 2- Retrograde Intubation. |
| 3- Blind Nasotracheal Intubation. | 4- Digitally Assisted Blind Oral Intubation. |
| 5- Manual Jet Ventilation. | 6- Submental (Submento-Tracheal) Intubation. |
| 7- Cricothyrotomy (Cricothyroidotomy). | 8- Tracheostomy. |

N.B.: **Trans-tracheal techniques** include techniques that enter the trachea directly as trans-tracheal jet ventilation, cricothyroidotomy, or tracheostomy.

Trans-laryngeal techniques include the techniques that pass through the glottis as conventional laryngoscopic intubation, flexible fiberoptic intubation, trans-laryngeal jet ventilation...etc.

A) Endotracheal Tube Guides:

a- Stylets:

They are used in difficult intubation to direct the tip of the tube inside the glottis.

1- Tube Stylet:

- It is introduced into the tube to change the direction of the tube's tip to be easily inserted in the glottis by using rigid laryngoscopy (figure 9-93).

2- Schroeder Stylet:

- It is a disposable plastic articulating stylet that allows the angle of the endotracheal tube to be adjusted to the correct angle, on performing direct laryngoscopy and tracheal intubation (figure 9-94).
- It can be used for both oral and nasal intubation.



Figure 9-93: A tube stylet



Figure 9-94: A Schroeder stylet

3- Parker Flex-it Stylet:

- It is similar to Schroeder Stylet; it allows the endotracheal tube curvature to be remotely adjusted during intubation with a thumb control. It can direct the tip of the endotracheal tube more anteriorly on using the GlideScope. It is usually used with a Parker flex-tip endotracheal tube (figure 9-95).



Figure 9-95: A Parker Flex-it stylet and its tube

4- Radlyn Stylet:

- It has a soft, tissue-dilating balloon incorporated onto a shapeable guide-tip that extends from the front end of the endotracheal tube. This prevents the endotracheal tube to catch on the laryngeal inlet anatomy as it passes over the guide, preventing its passage into the trachea.
- The Radlyn Stylet is placed inside the endotracheal tube and stabilized between the inflated dilating balloon and a unidirectional endcap. The endcap prevents the stylet from moving forward. The flexible guide-tip and the rest of the Stylet can be shaped as desired to facilitate insertion and placement of the endotracheal tube.

- The stylet's narrow guide-tip slips easily through the glottic opening while the tapered balloon further opens the tissue to the diameter of the endotracheal tube. A smooth, easy passage of the endotracheal tube into the airway is achieved. The new Radlyn Stylet offers greater intubation capabilities without any change in technique or the need for assistance (figure 9-96).



Figure 9-96: A Radlyn Stylet

b- Tube Introducers and Exchangers:

5- Eschmann Tracheal Introducer (Gum Elastic Bougie):

- It is 60-cm long, 15-French gauge stylet with a 40-degree curve about 3.5 cm from the distal tip i.e., with an angulated tip. There is a straight model without the angulated tip (figure 9-97).
- Uses: - It is useful in patients with anterior larynx or with limited mouth opening.
- Straight Eschmann tracheal tube guides are used for endotracheal tube exchange.



Figure 9-97: An Eschmann Tracheal Introducer (Gum Elastic Bougie)

6- Frova Intubating Introducer:

- It is 65-cm long (adult size) or 35 cm (pediatric size) with an angulated distal tip (as the gum elastic bougie). It has a hollow lumen, to accommodate a stiffening stylet, and an adaptor that permits ventilation via a breathing circuit or jet ventilation (figure 9-98).

7- Arndt Airway Exchange Catheter Set:

- It is 70 cm long. It has a hollow lumen and adaptor that permit ventilation via a breathing circuit or jet ventilation. It has a stiff wire guide and a bronchoscopic port for positioning. It has distal side-ports to ensure adequate air flow.
- It is used to exchange the endotracheal tube and laryngeal mask airway by using a fiberoptic bronchoscope (figure 9-99).

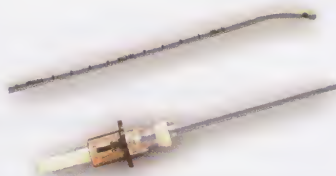


Figure 9-98: A Frova Intubating Introducer

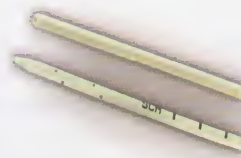


Figure 9-99: An Arndt Airway Exchange Catheter Set

8- Aintree Airway Exchange Catheter:

- It is 56 cm long with a lumen of adequate size (4.8 mm inner diameter) to **accommodate a fiberoptic bronchoscope**. There is an adaptor to allow ventilation by a breathing circuit. There are centimeter marks to facilitate accurate positioning (figure 9-100).

9- Cook Airway Exchange Catheter:

- It is 45 cm (pediatric size and tracheostomy tube), 83 cm (pediatric size), or 100 cm long that allows exchange of double lumen tubes. There is either a Luer lock connector or an adaptor to allow ventilation by a breathing circuit.
- There is also a **Soft tipped cook Airway exchange catheter** (figure 9-101).



Figure 9-100: Aintree Airway Exchange Catheter

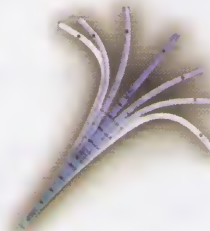
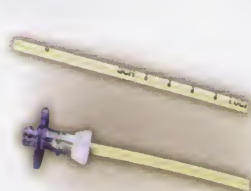


Figure 9-101: Cook Airway Exchange Catheter; the right catheter has a soft tip

10- Patil Two-Part Intubation catheter:

- It is 63 cm long, formed of two parts that can be assembled together. It is with an adaptor to allow ventilation. It can be used for endotracheal tubes with 7 mm ID or larger (figure 9-102).



Figure 9-102: A Patil Two-part Intubation catheter

11- Musa Muallem Tube Introducer:

- It is 75 cm long, with 4-6 mm outer diameter. It is soft like rubber, yet rigid enough not to kink on railroading the endotracheal tube over it.
- It has an inner channel for O₂ insufflation, suction, or jet ventilation.
- It has a rounded closed olive tip which is soft and flexible for about 2 cm long, decreasing the risk of mucosal injury during introduction. The tip is also curved with a 45 degree angle to be easily used with different types of laryngoscopes such as Macintosh, Bullard, or UpsherScope (figure 9-103).

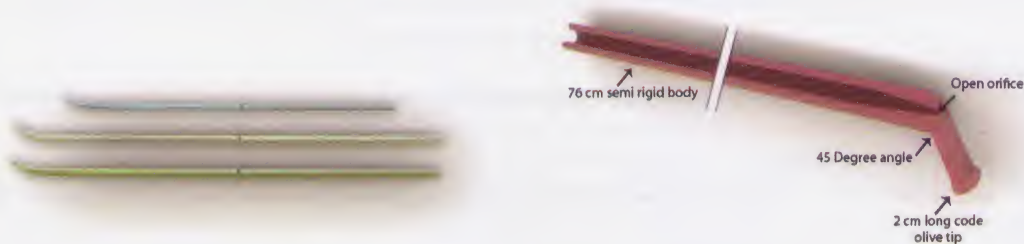


Figure 9-103: A Muallem Tube introducer

12- Rivier Introducer Airway:

- It is 83 cm long and with a lumen for oxygenation. It is for a single use (figure 9-104).

13- Mizus Endotracheal Tube Replacement Obturator (METTRO)

- It is flexible and soft with positioning marks. It has tapered atraumatic tip designed to facilitate tube exchange. It is 70 cm (pediatric size) and 80 cm (adult size) (figure 9-105).



Figure 9-104: A Rivier Introducer Airway



Figure 9-105: METTRO

N.B.: Role of Airway Exchange Catheters:

Airway exchange catheters increase success of re-intubation and O₂ insufflation. Airway exchange catheter can cause many complications e.g., perforation of the tracheobronchial tree, failure to pass an endotracheal tube over the catheter, or barotrauma when wrong size, type, or technique is used.

General Recommendations during Usage of Airway Exchange Catheters:

- Avoid small sized airway exchange catheters as they are liable for kinking.
- Match the mark of the airway exchange catheter with the centimeter markings on the endotracheal tube to avoid excessive advancement and carinal and bronchial injury.
- Use the airway exchange catheter with a hollow lumen to allow oxygenation.
- Advance the catheter gently with rotation and by laryngoscopy (if needed).
- Use silicone-based spray or a lubricant gel.
- Use capnography to assess tube position before removal of the airway exchange catheter.

c- Tube Introducers and Airways:**14- Cord Care™, Intubating Sheath:**

It facilitates tube insertion (figure 9-106).

15- Augustine Guide:

- The preloaded guide with an endotracheal tube is inserted blindly to rest on the hyo-epiglottic ligament. Aspiration of air through the stylet confirms tracheal placement (figure 9-107).

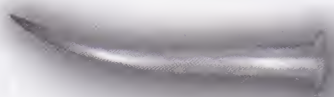


Figure 9-106: Cord Care Intubating Sheath

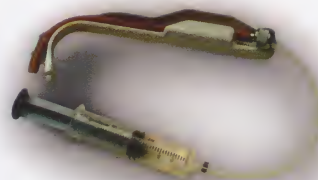


Figure 9-107: An Augustine Guide

16- Intubating Berman Guide:

- It can be used as an endotracheal tube can be inserted through which into the trachea blindly (figure 9-108).

17- Ovassapian Airway:

- It is similar to the intubating Berman guide as through which an endotracheal tube can be inserted into the trachea blindly (figure 9-109).

18- Williams Airway Intubator:

- It is a single use device with a cylindrical shape on the proximal half and an opening on the distal half (figure 9-110).

- It is indicated for use as: - an oropharyngeal airway,
- a means of intubating the trachea,
and - a guide for fiberoptic laryngoscope placement.
- 9 cm size is recommended for use with up to 7.5 mm ID endotracheal tubes.
10 cm size is recommended for use with up to 8.5 mm ID endotracheal tubes.



Figure 9-108: An Intubating Berman Guide



Figure 9-109: An Ovassapian Airway



Figure 9-110: A Williams Airway Intubator

19- Supraglottic Airway Laryngopharyngeal Tube (SALT):

It is inserted like an oropharyngeal airway, and then an endotracheal tube is passed through the center of the device. It eliminates the need for a laryngoscope (figure 9-111).



Figure 9-111: Supraglottic Airway Laryngopharyngeal Tube (SALT)

B) Lighted Stylets:

1- Trachlight (Lightwands):

- Design: It consists of 3 parts; a reusable handle, a flexible wand, and a stiff retractable stylet (3 sizes are available that accommodate endotracheal tubes from 2.5-10 mm ID) (figure 9-112).

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Figure 9-112: A Trachlight (Lightwands)

- Uses: - Cases in which bronchoscopy is difficult e.g., covering of the airway by blood or secretions.
- Conditions where fiberoptic bronchoscopy is not available.
- Patients with limited mouth opening, limited extension or flexion of the head, cervical spine instability, limited interincisor gap, poor dentition, severe overbite, or facial trauma.
- Technique: The device is advanced in the midline of the airway until a well-circumscribed glow is seen through the anterior surface of the neck. As the device is advanced further, the light is seen traveling

down the neck and disappears under the sternal notch. A diffuse glow indicates that there is more soft tissue being trans-illuminated and the device is in the esophagus rather than the trachea.

• **Contraindications:**

- Patients with oropharyngeal pathology e.g., laryngeal fractures, pharyngeal masses or abscess, or foreign body, as they are introduced blindly and may cause more damage.
- Patients with thick necks and dark skin.

2- Seeing Optical Stylet (SOS):

• **Design:** It is a reusable high resolution fiberoptic semi-malleable stainless-steel endoscope. It is available in adult and pediatric sizes. The adult size SOS requires a 5.5 mm ID endotracheal tube or a larger one. The pediatric size SOS requires 3.0-5.5 mm ID endotracheal tubes (figure 9-113).

• **Uses:** It is used instead of a fiberoptic bronchoscope.

• **Technique:** The endotracheal tube is mounted on the SOS and it is advanced through the upper airway just as a lighted stylet. The SOS offers the advantages of visualization of the airway structures as it is advanced. As with any fiberoptic endoscope, the view is dependent on the amount of space that is present. Maneuvers that increase the pharyngeal space (chin lift, jaw thrust, tongue traction) improve the field of view on using the SOS.

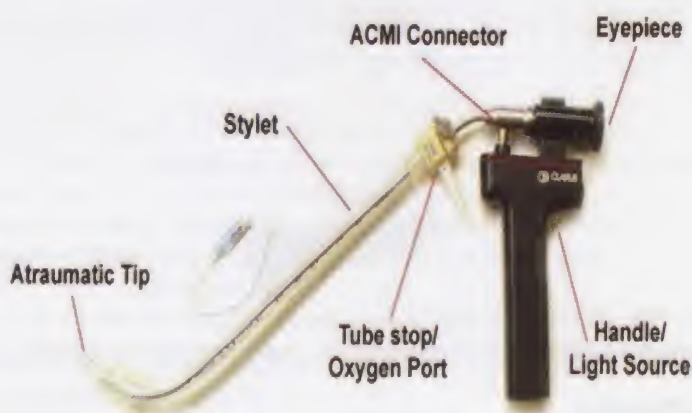


Figure 9-113: A Seeing Optical Stylet (SOS)

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3- Flexible Airway Scope Tool (FAST):

- As SOS, but its tip is atraumatic and easily adjusted by the hand to conform to the patient's anatomy (figure 9-114).

4- Bonfils Retro-molar Intubation Fiberscope (Levitan):

It is an optical stylet with a fixed distal curve. It allows a retro-molar approach to the difficult airway (figure 9-115).



Figure 9-114: A Flexible Airway Scope Tool (FAST)



Figure 9-115: A Bonfils Retro-molar Intubation Fiberscope (Levitan)

C) Rigid Laryngoscopes:

Besides the other types of laryngoscopes (discussed above), there are:

1- Flexible Tip or Levering McCoy Laryngoscope (Flipper) (Heine Blade):

- **Design:** It is a McCoy adaptation of the Macintosh blade with a hinged movable distal tip controlled by a lever at the proximal end that is triggered with the thumb of the anesthiologist's left hand during direct laryngoscopy (figure 9-116).
- **Uses:** for cases with large floppy infantile epiglottis.
- **Technique:** The laryngoscope is inserted into the vallecula (like the Macintosh blade) and then the lever is deployed to increase the lift on the hypo-epiglottic ligament.



Figure 9-116: A McCoy Flap tip blade

2- Flexiblade Laryngoscope:

- It is similar to the McCoy blade, but whole the blade (not only the tip) is flexed by pressing over a lever in the handle of the laryngoscope (figure 9-117).

3- Dörge's Emergency Laryngoscope Blade:

- It is a universal blade which combines features of both Miller and Macintosh blades. It is available in one size which is used for any patient > 10 kg body weight. It has 10 and 20 kg markings on the blade, and it is inserted into the oropharynx to the appropriate depth, which correlates with the patient's size (figure 9-118).



Figure 9-117: A Flexiblade laryngoscope



Figure 9-118: Dörge's Emergency Laryngoscope Blade

4- Patil-Syracuse Handle:

- It allows multiple locking positions of the attached laryngoscope blade (figure 9-119).
- N.B.: A Patil-Syracuse mask is discussed below.

5- Magboul Laryngoscope:

- It has a joint in the handle to flex the whole blade (figure 9-120).



Figure 9-119: A Patil-Syracuse handle



Figure 9-120: A Magboul Laryngoscope

6- IntuBrite Laryngoscope:

- Intubrite laryngoscope has a hyper-visualization system with a dual system of white and black lights (LED and Ultraviolet lights respectively). Both lights illuminate the vocal cords and cause them to brightly appear during intubation giving a near-3D structure differentiating hyper-visualization effect, thereby improving the efficacy of intubation.
- The Intubrite laryngoscope is accompanied with a phosphorescing stylet which is coated with a phosphorescent material that is activated under the black light, and clearly shows passage through the vocal cords.
- The Intubrite blade is constructed of stainless steel and lies at a 50-degree angle with the ergonomic aluminum handle. There are disposable blades with 7 different sizes.
- The Intubrite handle is curved to fix the handgrip and to deliver a better lift angle (figure 9-121).

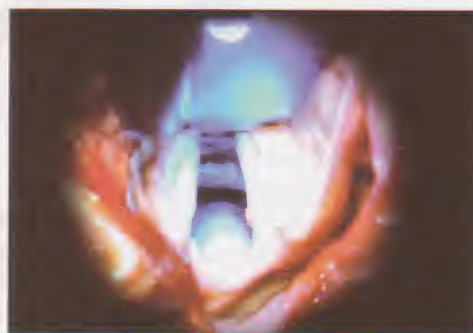


Figure 9-121: Intubrite with its stylet (left) and the laryngoscopic bright phosphorescent view

7- Viewmax Laryngoscope or Truview:

- It is a modified Macintosh laryngoscope blade that incorporates an unmagnified optic side port on a standard Macintosh blade that refracts image about 20° from the horizontal. Therefore, it allows direct view of the glottis from a point 1 cm behind the left tip of the blade and still allows the standard direct view (figure 9-122).

8- Trachview Videoscope:

The eye piece is with a cable. It is more convenient for the physician (figure 9-123).



Figure 9-122: A Viewmax Laryngoscope



Figure 9-123: A Trachview Videoscope

9- GlideScope:

• **Design:** It is a new video laryngoscope with a digital camera. It has an embedded anti-fogging mechanism and with LCD monitoring colored screen. It is an anatomically shaped, fixed-angle laryngoscope blade made of medical-grade plastic. The tip of the laryngoscope blade may be placed in the vallecula or used to lift the epiglottis directly (figure 9-124).

There is miniaturizing small size GlideScope called "Ranger" (figure 9-125) and GlideScope with disposable handle called "COBALT" (figure 9-126).

• **Technique:** An endotracheal tube, with a stylet angled to mimic that of the distal tip of the GlideScope, is advanced blindly until it can be visualized on the monitor, after which the tube is advanced into the trachea based on the image on the monitoring screen.



Figure 9-124: A GlideScope



Figure 9-125: A Miniaturizing GlideScope (Ranger)



Figure 9-126: A GlideScope COBALT

10- Macintosh Video Laryngoscope and X-lite Video Set:

• It is a Macintosh blade with a handle containing a control unit for an integrated wide-angle video camera and LCD screen and xenon light source (figure 9-127).

11- McGrath Series 5 Fully Portable Video Laryngoscope:

It is similar to Macintosh video laryngoscope. There is a camera and a display screen, which are fixed on a disposable optical blade (figure 9-128).



Figure 9-127: A Macintosh Video Laryngoscope



Figure 9-128: McGrath Series 5 Fully Portable Video laryngoscope

12- Pentax Laryngoscope:

It is a video laryngoscope, with a screen (figure 9-129).

13- AirTraQ Laryngoscope:

- It is a single use device. It is an anatomically shaped laryngoscope with 2 separate channels:
 - the optical channel: contains a high definition optical system
 - the guiding channel: holds the endotracheal tube and guides it through the vocal cords.
- It has a built-in anti-fog system and a low temperature light (figure 9-130).

14- Res-Q-Scope

It is similar to the AirTraQ and Pentax (figure 9-131).



Figure 9-129: A Pentax Laryngoscope



Figure 9-130: An AirTraq



Figure 9-131: A Res-Q-Scope Laryngoscope

D) Indirect Rigid Fiberoptic Laryngoscopes:

1- Bullard Elite Laryngoscope:

- **Design:** It has curved blades with elongated tip to help see the glottic opening. It can be used with a conventional battery-powered laryngoscope handle or with a fiberoptic light source. It is available in adult and pediatric sizes. It has an adjustable focus in the eyepiece. The blade contains a 3.7-mm channel for O₂ insufflation, suction, and instillation of local anesthetics. There are several interchangeable metal stylets (figure 9-132).
- **Uses:** patients with large tongues or whose glottic opening is very anterior.
- **Technique:** The laryngoscope, with an endotracheal tube loaded on the stylet, is advanced in the midline of the patient's pharynx until the glottic opening is brought into view, and the endotracheal tube is then advanced under direct visualization.



Figure 9-132: A Bullard Elite Laryngoscope

2- UpsherScope:

- **Design:** It has a semicircular C-shaped blade with a delivery slot along the right side of the device. It serves as an endotracheal guide and allows for easy removal of the scope after tracheal intubation. It can be used with a conventional battery-powered laryngoscope handle or with a fiberoptic light source. There is an adjustable eyepiece that can be immersed during cleaning (figure 9-133).
- **Uses and technique:** as Bullard Elite laryngoscope.

3- Wu Laryngoscope (WuScope):

- **Design:** It consists of a three-port bivalve scope that can be disassembled for removal after tracheal intubation. The laryngoscope blade is tubular, which helps generate space in the pharynx for a greater field of vision while minimizing contact of the fiberoptic system with pharyngeal secretions. It can be used with a conventional battery-powered laryngoscope handle or with a fiberoptic light source. It has a channel for O₂ insufflation, suction, and instillation of local anesthetics. It is available in two adult sizes (figure 9-134).
- **Uses:** patients with large tongues or whose glottic opening is very anterior.

• **Technique:** An endotracheal tube is loaded into the channel of the scope. Tracheal intubation is accomplished as with the other rigid laryngoscopes, followed by release and removal of the anterior portion of the bivalve and then removal of the posterior portion and handle following the curvature of the airway.



Figure 9-133: An UpsherScope



Figure 9-134: A Wu Laryngoscope (WuScope)

E) Supra-Glottic (Supra-Laryngeal) Ventilatory Devices

1- Laryngeal Mask Airway (LMA)

It was developed by **Archie Brain** (1988) (British).

Design:

It is reusable, made of silicone rubber (i.e., latex-free) and autoclavable. It consists of a wide-bore tube whose proximal end is connected to a breathing circuit with a standard 15-mm connector and whose distal end is attached to an elliptical cuff which is inflated by a pilot tube.

N.B.: Diameters of anesthetic connections: There are 3 diameters for anesthetic connections:

- 15-mm: It is the internal diameter of breathing circuits which fits the adaptor of the endotracheal tube.
- 22-mm: It is the outer diameter of breathing circuits which fits to the mask or the anesthetic reservoir bag.
- 30-mm: It is the diameter of the scavenging system connector; it large enough to decrease the resistance against patient's expiration.

Types:

- 1- **Classic (standard) LMA.**
- 2- **Flexible LMA:** It is armored, wire-reinforced LMA.
- 3- **Disposable (unique) LMA** (figure 9-135).

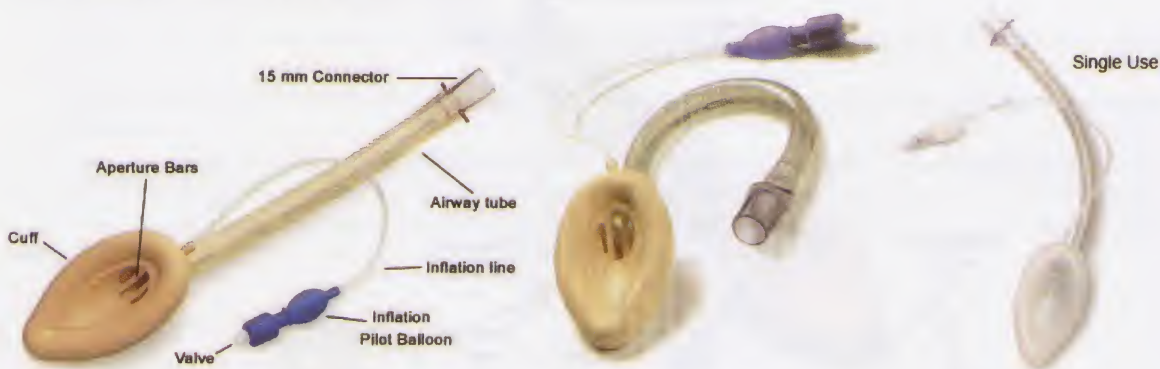


Figure 9-135: A Classic (standard) LMA (left), flexible LMA (middle), and single use LMA (right)

4- LMA-Fastrach (Intubating LMA) (ILMA) (Intavent):

- The two bars at the aperture of the regular LMA have been replaced by a single, movable epiglottic elevating bar that allows a smooth and unobstructed passage of an endotracheal tube as it emerges from

the rigid metal shaft of the LMA-Fastrach. The shaft is shorter in length, thus eliminating the need for a longer endotracheal tube in patients with long necks (figure 9-136).

- It has three sizes: - Size 3 for a small adult or a large child.
- Size 4 for a normal adult.
- Size 5 for a large adult.

The three sizes will accept a tube of up to 8 mm internal diameter.

- It is designed to be used with a straight silicone wire-reinforced cuffed endotracheal tube not exceeding 8 mm internal diameter capable of being passed through the ILMA including the pilot balloon and pilot balloon valve. The tube has atraumatic tip to minimize the risk of pharyngeal trauma.
- The tube may be placed into the trachea blindly or under direct vision using a suitable fiberoptic scope.
- It is recommended that the ILMA is removed once the tube is passed into the trachea. A stabilizing rod is available to keep the tracheal tube in place and slide the ILMA out of the mouth.



Figure 9-136: An ILMA

5- Gastric (Proseal) LMA (PLMA):

- It has a modified posterior cuff that extends onto the back of the mask to improve the laryngeal seal; therefore, allowing high positive pressure application. There is also a 2nd channel for gastric tube placement or passage of regurgitated fluid. This protects airway against aspiration (Figure 9-137). It is reusable. A disposable single use device is also available.

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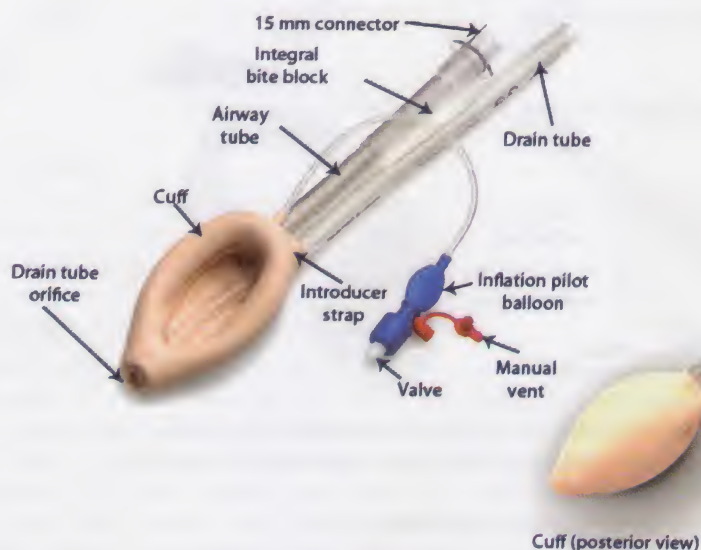


Figure 9-137: A PLMA

6- LMA C-Trach:

- It is a modified ILMA. It has the same anatomically curved stainless steel tube and is available in 3 mask sizes (3, 4, and 5).
- The epiglottic elevating bar has been modified to allow visualization of the larynx by means of fiberoptic bundles located within the bowl of the mask.
- A lightweight viewer is magnetically attached after the device has been inserted (figure 9-138).



Figure 9-138: A LMA C-Trach

Size:

Classic LMA Size	Weight of the Patient		Cuff Volume
1	< 5 kg	neonate/infant	2 - 5 ml
1.5	5 - 10 kg	infant	5 - 7 ml
2	10 - 20 kg	child	up to 10 ml
2.5	20 - 30 kg	child	up to 15 ml
3	30 - 50 kg	small adult (usually females)	up to 20 ml
4	50 - 70 kg	normal adult (usually males)	up to 30 ml
5	70 - 100 kg	large adult	up to 40 ml
6	> 100 kg	large adult	up to 50 ml

- **Gastric (Proseal) LMA (PLMA):** is available in sizes 2, 3, 4, and 5.
- **LMA-Fastrach (Intubating LMA) (ILMA) (Intavent):** is available in sizes 3, 4, and 5. The LMA Fastrach endotracheal tube are available in sizes 6.0, 6.5, 7.0, 7.5, 8.0 mm internal diameter.

Technique:

- After choosing the appropriate size and **checking** for cuff leaks before insertion, leave the cuff either **deflated or partially deflated**.
- **Lubricate** only the back side of the cuff.
- Ensure adequate anesthesia by either:
 - **general** anesthesia (propofol is preferred to thiopentone because it depresses pharyngeal reflexes better), or
 - **regional** nerve block for awake insertion (bilateral superior laryngeal nerve blocks and topical anesthesia).
- The patient's head should be in a **sniffing position**. LMA is held in the hand "**like holding a pen**" with the index finger to guide the cuff along the hard palate and down into the hypopharynx, until a resistance is felt. The longitudinal black line should always be pointing directly cephalad (i.e., facing the patient's upper lip) (figure 9-139).



Figure 9-139: Technique of LMA insertion

- **Inflate** with the correct amount of air as shown before.
- A correct position is indicated by movement of patient's chest with a gentle manual inflation or movement of the bag with patient's breathing.
- Obstruction after insertion is usually due to:
 - a down-folded epiglottis or distal cuff or
 - transient laryngospasm.
- In difficult cases, LMA insertion under direct visualization with a laryngoscope or fiberoptic bronchoscope may prove beneficial.
- A LMA introducer is available (figure 9-140).
- A bite block should be inserted beside the laryngeal mask airway (Figure 9-141).
- LMA is secured (to the middle of lips) with a tape or bandage.

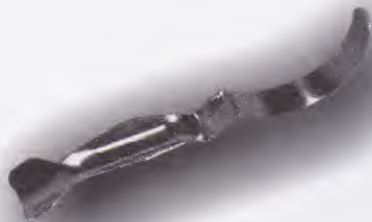


Figure 9-140: A LMA introducer



Figure 9-141: A bite block

N.B.: The ease of LMA insertion **does not correlate with Mallampati grade**. It appears that the position of the larynx has little effect on the LMA insertion. It has been suggested that the presence of an anterior larynx may make the LMA insertion easier.

• **Removal of LMA:** should be either when the patient is **deeply anesthetized** or after **awakening** and regaining of airway reflexes. Pharyngeal suction of secretions is usually not necessary before removing LMA. If suctioning is to be performed, it is important to ensure that an adequate level of anesthesia is present to avoid unnecessary airway manipulation. The cuff of the LMA may be either:

- deflated before removal,

or - left fully inflated to scoop out the secretions above the mask as it is withdrawn.

• At the end, the reusable LMA should be deflated evenly by a **special deflator** to avoid attaining an abnormal shape during the re-sterilization and reuse (figure 9-142).

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Figure 9-142: Variable shapes of cuff deflators

Indications:

a- Instead of the face mask in minor procedures; thus no need for the anesthesiologist's hand to support the mask.

b- Instead of the endotracheal tube (for spontaneous ventilation) with the following advantages:

1. **Pressor response** of intubation is avoided; therefore, it is preferred in patients with ischemic heart disease or hypertension.
2. Smooth induction and recovery are allowed:
 - This decreases the risk of increased **intraocular pressure**, so it is used in intraocular procedures.

- This decreases risk of increased **intracranial pressure**, so it is used in neurosurgery.

3. LMA is less invasive than intubation. It is preferred in **outpatient anesthesia**.

4. **Diagnostic fiberoptic laryngoscopy and bronchoscopy** can be done via the laryngeal mask allowing supplying patients with O₂.

N.B.: It can be used for mechanical ventilation with keeping airway pressure between 15-20 cm H₂O to avoid gastric insufflation and oropharyngeal leak.

c- In difficult intubation:

- It is used **as an airway** in case of "can not intubate, can not ventilate" because of its ease of use (its success rate is up to 99%).
- It is used **as a conduit** for an intubating stylet, bougie, ventilating jet stylet, flexible fiberoptic bronchoscope, or smaller diameter tubes (6.0 mm). The cricoid pressure is transiently released as it makes intubation via ILMA more difficult.
- It is used in **patients with cervical spine injury** because it can be applied in the neutral position.

d- In pulmonary medicine and thoracic surgery: LMA is used:

- to place tracheal and bronchial stents.
- to do fiberoptic guided percutaneous tracheostomy in intensive care units.
- to perform diagnostic fiberoptic laryngoscopy via LMA.
- as a conduit for Nd-YAG laser for ablation of tracheal and carinal tumors especially with difficult airway or high tracheal tumors.

e- Anesthesia outside the operating room: such as radiation therapy, diagnostic and interventional radiology, endoscopy, or cardioversion as there is no or slight pain and the anesthesiologist is away from the airway.

N.B.: It is recommended for operations 2-3 hours. If prolonged surgery is expected, intra-cuff pressure should be monitored and should not exceed 60 cm H₂O to avoid pressure injury of pharyngeal mucosa.

Contraindications:

- 1- **Pharyngeal** (glottic or subglottic) pathology as abscess, surgery, spasm, massive edema, tumor, hematoma, or any other cause of obstruction.
- 2- **Full stomach** or causes of delayed gastric emptying e.g., obstetrics, hiatal hernia or esophageal reflux.
- 3- High airway resistance e.g., **bronchospasm**.
- 4- **Low pulmonary compliance** e.g., obesity.

Both 3 and 4 require peak inspiratory pressure >20 cm H₂O which could increase gastric distension.

5- One lung ventilation.

Complications:

- 1- **Inflation of the stomach** especially when - peak inspiratory pressure exceeds 20 cm H₂O.
- the esophagus lies within the rim of the cuff.

Both **increase the risk of regurgitation**.

The incidence of regurgitation with LMA is 2: 10 000

The incidence of regurgitation with E.T.T is 1.7: 10 000 i.e., nearly the same.

2- **Sore throat** in 4-12% of patients.

3- **Coughing and laryngospasm** (as oropharyngeal airways).

4- **Risk of airway obstruction** in 25-50% of pediatrics and 10% of adults due to down-folding of epiglottis or distal end of the cuff.

5- **Trauma to the airway** (pharyngeal or laryngeal).

2- Air-Q Masked Laryngeal Airway:

• It is similar to the intubating laryngeal mask, but with a removable tethered connector providing a smooth insertion of a standard endotracheal tube; from sizes 5.5 to 8.5 ID (figure 9-143). It is either disposable or reusable. The air-Q laryngeal airway can be removed after insertion of the endotracheal tube by using the **removal stylet** without dislodging the endotracheal tube.

• **Air-Vu and air-Vu plus fiberoptic scopes:** They are rigid fiberoptic scopes used for visualizing endotracheal tube placement during intubation by the air-Q laryngeal airway. They are specifically designed to be used with the air-Q. The air-Vu plus is different from air-Vu by its curve which enhances proper alignment for improved visualization of the endotracheal tube placement (figure 9-144).



Figure 9-143: Air-Q masked laryngeal tube; reusable and disposable



Figure 9-144: Air-Vu (up) and air-Vu plus (down) with their light sources.
The left image shows the Air-Vu with the Air-Q inserted

3- Esophageal-Tracheal Combitube

Design:

- It consists of two fused tubes, each with a 15-mm connector on its proximal end;
 - The longer blue tube has an occluded distal tip that forces gas to exit through a series of side perforations.
 - The shorter clear tube has an open tip and no side perforations.
- There are two inflatable cuffs 85-100 cc proximal cuff and 10-15 cc distal cuff.

Technique:

- The combitube is usually **inserted blindly** through the mouth and advanced until the two black rings on the shaft lie between the upper and lower teeth.
- The 2 cuffs should be fully inflated after placement.
- Two possibilities are present after insertion of the tube:
 - a- Inserted into the esophagus: Ventilation via the blue tube (1) will force gases outside the side perforations and into the larynx. The other tube (2) can be used for gastric decompression (this is the most common possibility 99%).
 - b- Inserted into trachea: Ventilation through the clear tube will direct gas into the trachea (figure 9-145).

Advantages: (over LMA)

- It provides a better seal and better protection against gastric regurgitation and aspiration.
- It is used mainly in emergency medical management and requires minimal training.

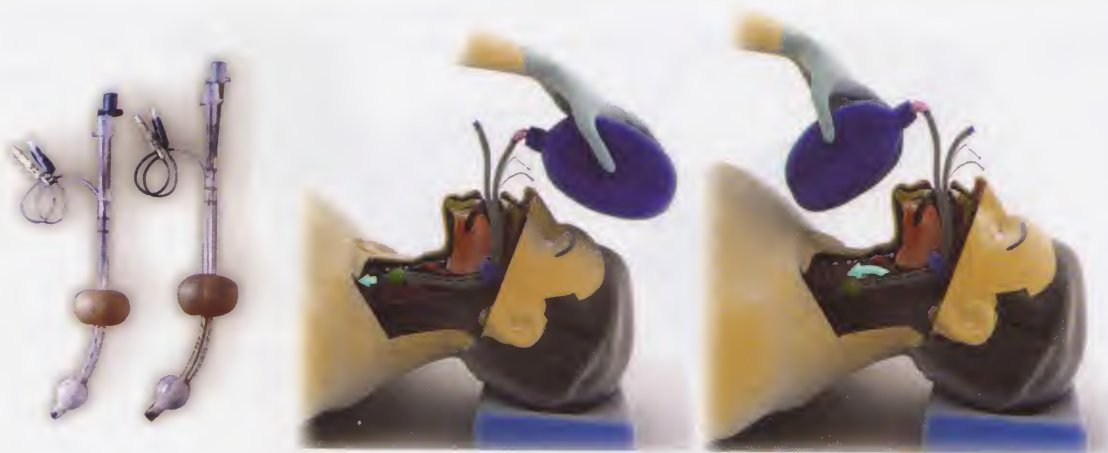


Figure 9-145: A Combi-tube

Disadvantages: (over LMA)

1- It is available **only in two disposable adult sizes:**

- The 37-French gauge small tube for adult patients between 120-180-cm height.
- The 41- French gauge tube for adult patients taller than 180 cm.

N.B.: All double lumen tubes such as combi-tubes or tubes that are used for one lung ventilation e.g., Robertshaw's tubes have no infant and small children sizes because the lumen will be very small increasing the resistance against ventilation as the radius of the tube is a very important factor determining the resistance according to the **Hagen-Poiseuille formula**.

$$\dot{Q} = \frac{\Delta P \times r^4 \times \pi}{\eta \times L \times 8}$$

Where, \dot{Q} represents the flow.

ΔP represents the pressure gradient.

r represents the radius.

η represents the viscosity.

L represents the length of the tube.

2- The side perforations prevent the use of the combi-tube as a guide for flexible fiberoptic bronchoscopy or intubation with the standard endotracheal tube.

3- As it has a blind end obstructing the esophageal inlet, **esophageal rupture** may occur in case of vomiting.

Contraindications:

1- **Pharyngeal** (glottic or subglottic) pathology as abscess, surgery, spasm, massive edema, tumor, hematoma, or any other cause of obstruction.

2- **Esophageal pathology** or a history of caustic substance ingestion as esophageal perforation has been reported.

3- Patients with an **intact gag reflexes**.

4- Patients **less than 120-150 cm tall**.

N.B.: Rusch Easytube Double Lumen Tube:

It is similar to the combi-tube with also two adult sizes only (figure 9-146).

4- Pharyngeal-Tracheal Lumen Airway (PTL Airway)

- It is similar to Combi-tube; it is a latex-free, double lumen tube that can deliver effective ventilation to the patient whether the device is placed in the trachea or esophagus.

- It requires no syringes to inflate the airway balloons and has an integrated bite block to keep the airway open (figure 9-147).



Figure 9-146: A Rusch Easytube Double Lumen Tube

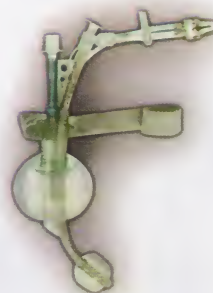


Figure 9-147: Pharyngeal-Tracheal Lumen Airway (PTL Airway)

5- Laryngeal Tube:

Design:

- It is a multi-use, latex-free, single-lumen silicon tube with an oropharyngeal and a blind distal esophageal low pressure cuffs. The blind distal cuff at the tip occludes the esophagus, protecting against aspiration. It has a ventilatory outlet that allows the air/O₂ to reach the trachea. It is available in 6 sizes (0-5) for infants, children, and adults because it is formed of a single lumen (figure 9-148).

Uses:

- It is used for spontaneous or positive pressure ventilation during routine or emergency airway management.

Technique:

- It is passed **blindly** into the pharynx as the combi-tube until a resistance is felt, then the two cuffs are inflated.

Disadvantages:

- As it has a blind end obstructing the esophageal inlet, esophageal rupture may occur in case of vomiting; therefore, **Double Lumen Laryngeal Tube S (LT Suction or LTS)** has recently been developed. It has a second esophageal lumen posterior to the respiratory lumen allowing suctioning of gastric contents. This second lumen is not for ventilation as in Combi-tube.

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Single lumen tube



Double lumen tube with drain tube



Figure 9-148: A laryngeal tube (LT) (left), a laryngeal tube S (LTS) (middle), and an inserted laryngeal tube (right)

6- Esophageal Obturator Airway:

- It is blocked at its distal end which enters the esophagus (not the trachea) and by its cuff air is not allowed to enter the stomach. Air enters the trachea through side ports above the distal cuff.
- It is more easily placed by less experienced personnel in unconscious patients so that effective resuscitation can be done anywhere under almost any condition.
- Disadvantages:
 - Inadequate ventilation.
 - Insertion into the trachea is as disastrous as esophageal intubation.
 - Risk of esophageal perforation especially if there is an esophageal trauma or disease.
- It should be replaced by an endotracheal tube as soon as possible.

7- Esophageal Gastric Tube Airway:

- It is similar to the esophageal obturator airway, but there is an access to the stomach by a gastric tube (figure 9-149).



Figure -149: An esophageal obturator airway (right) and an esophageal gastric tube airway (left)

8- Pharyngeal Airway X-press (PAX):

- It is a single use, latex-free, rigid curved tube with an anatomically shaped gilled tip at its distal end that seats at the cricopharyngeus muscle. It has a large volume - low pressure pharyngeal cuff with a ventilatory outlet (hooded window) (figure 9-150).
- It is placed blindly and protects against aspiration.
- Its lumen is large enough to accommodate up to a 7.5-mm endotracheal tube (if used as a conduit).

9- Cobra PLA (Peri-laryngeal Airway):

- It is a single-use soft and flexible tube with large internal diameter with a tapered straight tip. It has a high volume-low pressure oropharyngeal cuff (figure 9-151).
- It is placed blindly and protects against aspiration.
- Its lumen is large enough to accommodate up to an 8-mm endotracheal tube (if used as a conduit).



Figure 9-150: A Pharyngeal Airway X-press (PAX)



Figure 9-151: Cobra PLA

10- Cuffed Oro-Pharyngeal Airway (COPA)

It is discussed above.

11- Glottic Aperture Seal Airway (Soft Seal) (Vital Seal):

- It is similar to the disposable LMA. It is a disposable single-lumen latex free laryngeal mask that forms an airway seal with a sponge-like distal tip, but differs in its one-piece design, softer cuff, and in lack of a step between the tube and the cuff (figure 9-152).
- A plastic insertion blade lifts the epiglottis as the tube is inserted.

12- Streamlined Pharynx Airway Liner (SLIPA):

- It is a disposable supra-glottic airway designed to seal without the use of an inflatable cuff. It comprises a hollow blow-moulded soft plastic airway shaped to form a seal in the pharynx (figure 9-153).
- Being hollow, liquid entrapment is possible and this may provide effective protection against aspiration.



Figure 9-152: A Glottic Aperture Seal Airway



Figure 9-153: SLIPA

13- i-GEL Airway:

- i-gel is a single use supra-glottic airway with an anatomically designed mask made of a gel-like thermoplastic elastomer. It has features designed to facilitate insertion, minimize tissue compression, and maintain stability of position after placement.
- It also has features designed to separate the gastro-intestinal and respiratory tracts; an airway channel connected to a 15 mm port for ventilation and a gastric channel enabling access to and from the upper gastro-intestinal tract and through which a gastric tube may be passed (figure 9-154).
- It has also a hard piece at its proximal end that prevents biting the i-gel by teeth.

14- Cuffed Pharyngeal Tube:

- It reopens the airway by lifting the tongue and epiglottis up off the floor of the pharynx as in cases of loss of consciousness e.g., trauma (figure 9-155).



Figure 9-154: An i-gel airway



Figure 9-155: A cuffed Pharyngeal Tube

F) Special Airway Techniques:

1- Flexible Fiberoptic Intubation:

Design:

- It has 3-4 bundles:
 - **One image bundle** of glass fibers each consisting of 10 000- 15 000 fibers. The bundle provides a high resolution image
 - **One or two light source bundles** which transmit light from the light source.
 - One channel for aspiration, suctioning, insufflation of O₂, or instillation of local anesthetics (figure 9-156).
- It is available in adult and pediatric sizes.

Technique:

- Flexible fiberoptic intubation can be performed whether the patient is anesthetized or awake with airway block with local anesthesia and sedation (as above).
- **Anti-sialagogue** e.g., glycopyrrolate should be given as before.
- **Patient position:** It can be either:
 - **Sitting position:** where the patient sits up with the operator in front. This prevents the tongue and pharynx from collapsing backwards and obstructing the view. It also prevents any secretions from pooling at the back of the oropharynx.
 - or ◦ **Normal supine position:** The operator stands as in the usual intubating position.

a- Nasal Fiberoptic Intubation:

It is **easier** and associated with less gag reflex, **but more bleeding** may occur.



Figure 9-156: A bronchoscope (right) and the tip of a fiberoptic laryngoscope showing a channel (through which a catheter is passed), fiberoptic image bundle, and two light source bundles (left)

- Both nostrils are prepared by vasoconstrictor drops.
 - Adequate patient ventilation and oxygenation should be ensured, confirmed by capnography and pulse oximetry. This is achieved by:
 - O₂ insufflation via the aspiration channel of the bronchoscope.
 - A large nasal airway e.g. I.D. 7-8. It can be inserted in the contralateral nostril which is connected to a breathing circuit and 100% O₂.
 - In unconscious patients (who are not breathing), close the mouth by a tape and connect the nasal airway to a breathing circuit for controlled ventilation.
 - A lubricated endotracheal tube is inserted and advanced in the other nostril. The lubricated bronchoscope is then introduced via the tube. When its tip passes through the distal end of the endotracheal tube, the epiglottis or glottis should be visible. Then the tip of the bronchoscope is manipulated to pass via the abducted cords.
 - In difficult cases, having an assistant who thrusts the jaw forward or applies cricoid pressure may improve visualization. Even with good anesthesia, a violent cough occurs when the bronchoscope enters the trachea.
 - Once in the trachea, the scope is advanced to visualize the carina. The presence of tracheal rings and carina is a proof of proper positioning. Then the tube is slipped over the fiberoptic shaft.
 - Proper endotracheal tube position is confirmed by viewing the tip of the tube above the carina before the fiberoptic scope is withdrawn.
- b- Oral Fiberoptic Intubation:
- It can be done, but it is **more difficult** because the fiberscope is not anatomically directed towards the glottis.
 - The fiberscope is introduced via an **endoscopic oral airway or bite block** to protect the device, prevent dorsal displacement of the tongue and keep the device in the midline (figure 9-157).
 - **Patil-Syracuse mask or Endoscopy mask** (figure 9-158): is designed with a port that will accommodate an endotracheal tube and a fiberoptic bronchoscope through a diaphragm. This device allows for spontaneous or controlled ventilation while fiberoptic nasal or oral intubation is being performed.



Figure 9-157: A bite-block (left) and an endoscopic oral airway (right) for oral bronchoscopy



Figure 9-158: An Endoscopy mask

N.B.: The bronchoscope can be used to assess LMA insertion (figure 9-159).

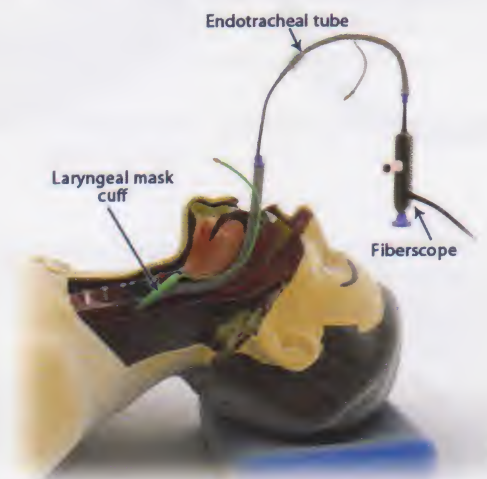


Figure 9-159: LMA-assisted fiberoptic intubation

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Indications of Fiberoptic Intubation:

- 1- Known or suspected difficult intubation.
- 2- Known or suspected cervical cord injury or cervical instability.
- 3- Morbid obesity.
- 4- A patient with full stomach in whom difficult intubation is anticipated.

Contraindications:

- 1- Uncooperative patients.
- 2- Lack of time as this technique is **not used in emergency situations**.
- 3- Hemorrhage in the upper airway.
- 4- Severe stridor secondary to peri-laryngeal tumor.
- 5- Allergy to local anesthetics.
- 6- Any thing that impinges on upper airway size and decreases the space around the scope e.g., edema of the pharynx or tongue, infection, hematoma, or infiltrating mass.

2- Retrograde Intubation:

Technique:

- The airway is anesthetized as described above in awake intubation.
- A guidewire or epidural catheter (via a **Tuohy needle**) is introduced through the **cricothyroid membrane**. Correct positioning is confirmed by the aspiration of air. It passes retrogradely up to oropharynx, then to the mouth or the nose.
- Then an endotracheal tube is railed over the catheter into the trachea.
- The guidewire and introducer are withdrawn from above whilst applying forward pressure on the tube.

- Cook (UK) makes a **commercially available retrograde intubation kit** for use with endotracheal tubes of internal diameter 5 mm or larger (figure 9-160).
- Recently, Arndt Airway Exchange Catheter can be used.
- The bronchoscope can be used to assess retrograde intubation (figure 9-161)

Uses:

It is mainly indicated in bleeding or in limited mouth opening or neck movement.



Figure 9-160: Retrograde intubation and the Cook kit

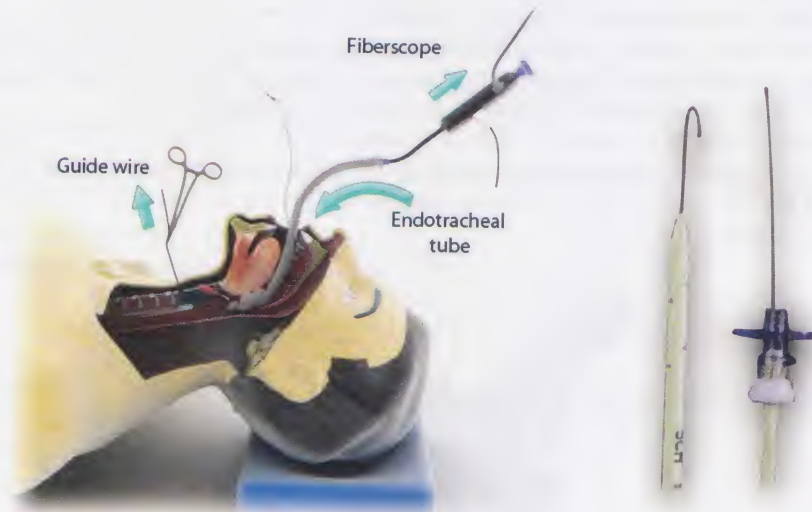


Figure 9-161: Retrograde fiberoptic intubation. The tip of the catheter and the guide-wire appears

3- Blind Nasotracheal Intubation:

It is an old technique, but still used in some circumstances.

Technique:

- **The nasal mucosa** should be vasoconstricted (if time permits) to decrease discomfort and bleeding.
- **An endotracheal tube** should be lubricated with lidocaine jelly and deformed for a few minutes to exaggerate its curvature.
- **The patient's head** should be in the sniffing position.
- The tube is introduced gently via the nostril perpendicularly to the face. Air movement through the tube should be continually felt, heard (e.g., by Burden nasoscope) (figure 9-162) or monitored by capnography or movement of the bag if the tube is attached to an anesthesia breathing circuit.
- The tube is advanced during inspiration. If the patient's respiration continues, but no air flow is detected via the tube, the tip has passed the glottis and now is in the esophagus. Therefore, withdraw the tube and advance it again.
- Breath-holding and coughing indicate close proximity to the larynx.
- If the tube does not easily enter the trachea, several maneuvers are done:
 1. A stylet bent to resemble a hockey stick.
 2. Extension of the head to move the tip of the tube anteriorly.
 3. Rotation of the head to move the tip of the tube laterally.

4. Laryngeal or cricoid pressure.
5. Inflation of the tube's cuff in the hypopharynx may guide the tip anteriorly.
6. If the tube persistently slips into the esophagus, voluntary tongue protrusion will inhibit swallowing and may move the tongue and the tube anteriorly to the trachea.



Figure 9-162: A Burden nasoscope

4- Digitally Assisted Blind Oral Intubation:

Uses:

- It can be performed in any patient, but it is easier in smaller adults and pediatric patients. It is the technique of choice for infants with hypoplastic mandible, especially if the blind nasal technique is undesirable or unsuccessful and appropriate fiberoptic equipment is unavailable.

Technique:

- After anesthesia either general or local/topical with i.v. sedation, the anesthesiologist, standing to the right of the infant, turns toward the head of the table and leans sideways over the patient.
- The gloved left index finger, lightly coated with 5% lidocaine ointment, is advanced posteriorly over the surface of the tongue in the midline. The palpating finger is curved naturally around the tongue, to lie at once over the glottis where the epiglottis and paired arytenoids are palpated easily.
- The endotracheal tube, held like a pencil in the right hand, is then advanced along the left index finger until its tip is felt to lie between the glottis and finger tip. With slight additional advancement of the tube, its end is pushed into the glottis with a flexion motion of the left index. Direct palpation confirms successful intubation (figure 9-163).



Figure 9-163: Digitally assisted blind oral intubation

5- Manual Jet Ventilation:

It is a device that applies the oxygen under pressure. The jet injector such as **Sanders jet injector** (introduced in 1967), or **Enk oxygen flow modulator** is connected to a catheter which is applied either trans-tracheally (i.e., from the front of the neck to inside the trachea) or trans-laryngeally (i.e., from the mouth, via the glottis, to inside the trachea as usual intubation).

It can be connected to a side port of the laryngoscope during endoscopic laryngeal or tracheal surgery (figure 9-164).

Technique:

- During inspiration (1-2 seconds), the jet pressure increases gradually, starting with:
 15-20 psig in adults.
 5-10 psig in infants and children.
- Psig = Pound square inch gram.
- Then the pressure increases gradually until adequate chest rise and fall is noted (usually 30-50 psig). While the O₂ source is directed through the glottic opening in trans-laryngeal jet ventilation, it entrains room air into the lung (**Venturi effect**).
- Expiration is allowed passively in (4-6 seconds).

- It is important to **monitor the chest wall motion constantly** and to **monitor the respiration by auscultation**, for proper tidal volume assessment and to allow sufficient time for exhalation to avoid air trapping.



Figure 9-164: Two different shapes of manual jet ventilation (left) and different sized-needles for jet ventilations (right)

Types:

- Trans-tracheal jet ventilation:** is used mainly during **emergency airway management** as in “cannot intubate, cannot ventilate scenario”. It is a life-saving measure. Manual jet injector is attached to a catheter which is introduced inside the trachea through the cricothyroid membrane.
- Trans-laryngeal jet ventilation:** is used mainly during **laryngeal or tracheal surgery**. It is not suitable during emergency airway management.

Complications:

- Air trapping and barotrauma resulting in pneumothorax, pneumo-mediastinum or subcutaneous emphysema.
- Drying of mucosal surface.
- In trans-laryngeal jet ventilation:**
 - Aspiration of resected material.
 - Complete respiratory obstruction.
 - Gastric dilatation with possible regurgitation.

Contraindications:

- In trans-tracheal jet ventilation:** as it is life saving, no contraindication is present except difficult cannula insertion e.g., a large goiter or very thick neck.
- In trans-laryngeal jet ventilation:**
 - Airway obstruction without tracheostomy.
 - Obesity.
 - Increased risk of aspiration.
 - Advanced chronic obstructive airway diseases.
 - Presence of a foreign body as jet ventilation pushes it more distally which increases difficulty of removal.

6- Submental (Submento-Tracheal) Intubation:

Technique:

- At first, oro-tracheal intubation is done, with reinforced tracheal tube with a detachable connector, using standard general anesthesia technique.
- A 1.5-2 cm incision is made in the submental region parallel and medial to the inferior border of the mandible. The incision is extended intraorally by blunt dissection with curved artery forceps.
- The intraoral opening is lateral to the submandibular and sublingual ducts. Thus a submental tunnel is created. The tracheal tube is then briefly disconnected from the breathing circuit and the tube connector removed from the tube. The pilot balloon followed by the tracheal tube is gently pulled out through the submental tunnel.
- During this step tracheal tube is stabilized intraorally manually or by A Magill forceps. The tube connector is reattached and tracheal tube is reconnected to the anesthesia breathing circuit. The tube is fixed in its position with sutures.
- At the end of the surgical procedure, submento-tracheal intubation is converted back to oro-tracheal one. The submental incision is closed not so tightly with interrupted skin sutures so as to allow certain degree of drainage (figure 9-165).

Uses:

- It is performed instead of tracheostomy mainly in patients with **faciomaxillary trauma**, especially when accompanied by fracture nose or fracture base of the skull (as nasotracheal intubation is contraindicated), where intraoperative maxillo-mandibular fixation to restore dental occlusion is needed.

Advantages:

- It is more cosmetically accepted than tracheostomy.
- It can be used in cases in which nasotracheal intubation is contraindicated.

Disadvantages:

- It is not a technique for emergency airway.



Figure 9-165: A patient with submental intubation

7- Cricothyroidotomy (Cricothyrotomy):

It is sometimes called mini-tracheostomy. It is 3 types:

a- Needle Cricothyrotomy:**Uses:**

- Emergency conditions as “cannot intubate cannot ventilate scenario” because it is quicker and easier than other techniques.
- Other cases of difficult intubation e.g., severe facial trauma.

Technique:

- It is performed by using large i.v. cannula-over-needle gauge 12-14 G. It needs special connections, with a low compliance tube, to allow the usage of a high pressure source O₂ (50 psi), to generate sufficient gas flow such as **trans-tracheal jet ventilation**.
- The cannula is introduced in the midline of the cricothyroid membrane. Proper location is confirmed by aspiration of air (figure 9-166).
- It is replaced later by tracheostomy.

Complications:

a- Acute: bleeding, esophageal rupture, stomal infection, and aspiration.

b- Chronic: tracheomalacia, sub-glottic or tracheal stenosis, tracheo-esophageal fistula due to pressure necrosis of the posterior tracheal wall, and vocal cord changes.

These are besides the complications of trans-tracheal jet ventilation.

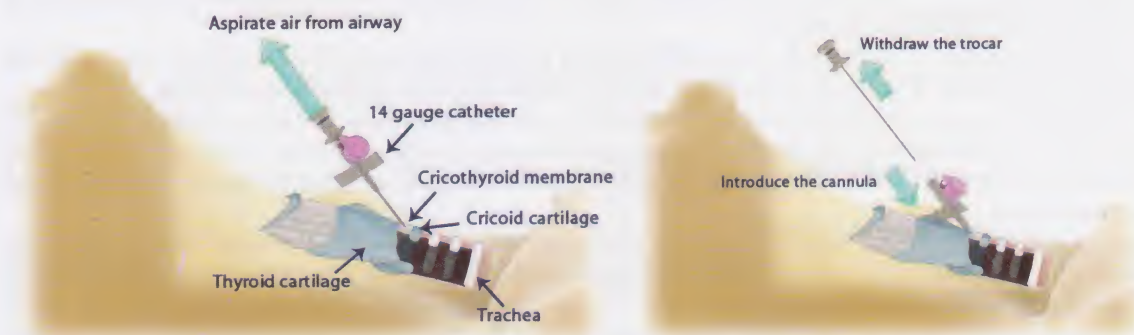


Figure 9-166: Needle cricothyrotomy

b- Percutaneous Cricothyrotomy:

• There is a number of commercial kits available. They use the **Seldinger technique** (i.e., a cannula over a guide).

For example:

- Melker Emergency Cricothyrotomy Catheter Set: It is with a high volume, low pressure cuff.
- Patil Emergency Cricothyrotomy Catheter Set.
- Quicktrach Emergency Cricothyrotomy kit for adult and pediatric patients.
- Nu-trache cannula is large enough to allow adequate ventilation with a self-inflating resuscitation bag (figure 9-167).



Figure 9-167: Emergency Cricothyrotomy Catheter Sets; Melker, Nu-trache, Quicktrach, and Patil (from left to right in order)

c- Surgical Cricothyrotomy:

It is performed by making an incision with a scalpel followed by endotracheal tube insertion.

8- Tracheostomy (or Tracheotomy):

It is a technique of creating a hole in the trachea.

There are many techniques:

a- Percutaneous Dilatational Tracheostomy: (the most commonly used technique).

It is **more preferred** and advantageous than surgical tracheostomy because it produces **fewer complications**.

Technique:

- After monitoring, consent, and infiltration with 1% lidocaine, a 1-1.5 cm skin incision at the midline crease is done. The subcutaneous tissues are bluntly-dissected to the anterior tracheal wall.
- The endotracheal tube tip is withdrawn to the level of the vocal cords. The trachea is then punctured in the midline with 14 G needle between the 1st and 2nd tracheal cartilages (or lower), allowing guide-wire insertion.
- The stoma is created by two methods:
 - **Ciaglia technique:** The stoma is created by dilatation to 32-36 French, and the tracheostomy tube is introduced over an appropriate-sized dilator.
 - **Schachner-Ovill technique:** The stoma is created by a guided forceps dilating tool, and the tracheostomy tube is introduced through the open dilating tool.
 - **Griggs dilating forceps kit** for percutaneous tracheostomy: The Griggs forceps allows tracheal stoma dilatation with minimal trauma (figure 9-168).
- Confirmation of the correct position is done by:
 - End-tidal CO₂ monitoring (it also assesses adequate ventilation).
 - Fiberoptic bronchoscopy (it also assesses presence of trauma to the posterior tracheal wall).
- **Tracheostomy tubes should be replaced every 5-7 days or when indicated.**



Figure 9-168: A percutaneous tracheostomy introducer set; Ciaglia (left) and Griggs (right)

b- Trans-Laryngeal Tracheostomy: (a new technique)

It is done through the larynx. It is safe and can be performed at the bedside and in patients who are coagulopathic. It is either:

a- Fantoni trans-laryngeal tracheostomy technique:

- It is less invasive because the stoma is performed outwards and the tracheal rings are simply divaricated. It uses a **rigid tracheoscope**.

b- Modified Fantoni technique:

- It uses the **fiberoptic bronchoscope** in place of rigid tracheoscope.
- It uses a J-shaped wire.
- It uses a small endotracheal tube positioned coaxially to ventilate the patient during introduction of the tracheostomy tube.

c- PERCUTWIST:

- It is a newly developed single-step-rotational dilation tracheostomy technique.
- The dilator has a hydrophilic coating on a tapping thread and is designed like a self-tapping screw, allowing access to the trachea without the need of pushing the instrument towards the tracheal wall offering controlled rotating dilation.

c- Surgical Tracheostomy:

It is **more invasive** and with more complications; therefore, it is only done in elective cases.

Indications of Surgical Tracheostomy:

- 1- Upper airway obstruction.
- 2- Need for long-term mechanical ventilation. **Conversion from the endotracheal tube to tracheostomy** is done usually **after 2-3 weeks** of intubation, but **recent studies** advocate **shorter periods**.
- 3- Access for frequent suctioning.
- 4- Helping weaning of mechanical ventilation.
- 5- Treatment of severe obstructive sleep apnea when CPAP is not tolerated.

N.B.: There are **no absolute contraindications to tracheostomy** as it is lifesaving.

Complications: They are as these of cricothyroidotomy (see above).

Accidental dislodgement of tracheostomy tube before the stoma tract is mature (which takes about one week) the tract closes quickly, and blind reinsertion of the tube can create false tracts. To minimize this risk, the patient should be re-intubated orally before attempting to reinsert the tracheostomy tube.

Maintenance of Tracheostomy:

- 1- Since the upper air passages have been bypassed, artificial humidification is required.
- 2- Cough is less effective without a functioning larynx, so regular tracheal suction will be necessary.
- 3- Natural laryngeal PEEP is lost with a tracheostomy.
- 4- The risk of basal atelectasis can be overcome with CPAP or attention to respiratory exercise that promote deep breathing.
- 5- After 3-5 day, the tracheostomy tube can be safely replaced.
- 6- Before removing the tube, ensure the upper airway is patent, either by allowing the patient to exhale passed an occluded tracheostomy tube or by visualization.

Types of Tracheostomy Tubes:

1- Standard Tracheostomy Tube with High Volume, Low Pressure Cuff (figure 9-169).

2- Fenestrated Tube with or without Cuff:

It is closed during normal breathing, but provides intermittent suction access.

3- Fenestrated Tube with Inner Tube:

As above, but the inner tube facilitates closure of the fenestration during intermittent mechanical ventilation (figure 9-170).



Figure 9-169: A Tracheostomy tube with cuff (right) and without cuff (left)



Figure 9-170: A fenestrated tracheostomy tube (left) with a fenestrated inner tube (middle) and an unfenestrated inner tube (right)

4- Fenestrated Tube with Speaking Valve:

Inspiration is allowed through the tracheostomy to reduce dead space and inspiratory resistance, and expiration is done through the larynx via the fenestration, allowing speech together with the advantages of laryngeal positive end expiratory pressure (figure 9-171).

5- Tracheostomy Tube with Adjustable Flange:

It accommodates extreme variations in skin-to-trachea depth, while ensuring the cuff remains central in the trachea (figure 9-172). It is suitable for patients with deep-set tracheas and allows stoma hygiene as the flanges are movable.

6- Pitt Speaking Tube:

It is a non-fenestrated cuffed tube used for continuous mechanical ventilation and airway protection with a port to direct airflow above the cuff to the larynx.

7- Passy-Muir Speaking Valve:

It is an expiratory occlusive valve which is placed onto the tracheostomy tube to permit inspiration through the tracheostomy and expiration through the glottis. The tracheostomy tube cuff must be first deflated. The valve allows phonation, facilitates swallowing, and may reduce aspiration. Few studies have suggested that it may reduce the work of breathing. The potential tidal volume drop through cuff deflation makes this valve only suitable in those patients requiring no (or relatively low level) invasive ventilatory support.

8- Silver Tracheostomy Tube:

It is a cuffed tube used occasionally in the practice of otorhinolaryngology to maintain a tracheostomy fistula (figure 9-173).



Figure 9-171: A fenestrated tube with speaking valve



Figure 9-172: A tracheostomy tube with adjustable flange



Figure 9-173: A silver tracheostomy tube

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Web Site

- <http://magboul.multiply.com/>

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|---|---|
| <ul style="list-style-type: none"> • Physiological changes during pregnancy • Utero-placental blood flow (UBF) • Placental transfer of anesthetic agents • Fetal affection of drugs given to the mother • Lactation and drugs in obstetric anesthesia • Effects of anesthetic and other relevant drugs on uterine activity and labor • Physiology of pain in labor • Analgesia for vaginal delivery • Anesthesia for cesarean section (CS) • Risks of anesthesia for cesarean section • Anesthesia for high risk (complicated) obstetrics <ul style="list-style-type: none"> - Pre-eclampsia and Eclampsia - Maternal hemorrhage during labor - Premature or preterm labor - Multiple gestation | <ul style="list-style-type: none"> - Maternal heart diseases - Diabetes mellitus with pregnancy - Amniotic fluid embolism - Ectopic pregnancy - Acute fatty liver of pregnancy • Other minor obstetric procedures • Postpartum tubal ligation • Anesthesia for non-obstetric surgery in pregnant patients • Anesthesia for assisted reproductive technologies (ART) <ul style="list-style-type: none"> - Ovarian hyper-stimulation syndrome • Intensive care unit (ICU) considerations of pregnant patients • Anesthesia for gynecological surgery |
|---|---|

The care of the pregnant patient is necessarily the care of two patients (the parturient and the fetus). Although care of the mother is the primary concern in most circumstances, attention also must be paid to fetal health and well-being.

Physiological Changes during Pregnancy

There are three major changes that affect all systems in the pregnant female. They include:

- A **hyperdynamic state** which increases the respiratory and cardiovascular functions.
- A **big gravid uterus** which produces pressure effects on the surrounding structures.
- **Increased progesterone** during pregnancy which produces sedation to the mother and **relaxation to the smooth muscles** and ligaments. This produces the vasodilatation and relaxation during labor.

1- Central Nervous Changes:

A **progressive decrease** in the minimal alveolar concentration (MAC) for all general anesthetic agents down to **40% at term** is observed because:

- Progesterone has a sedating effect.
- *β endorphin increases during labor.*

Therefore, a pregnant female is easily subjected to loss of consciousness by a small concentration of inhalational anesthetics (less than the non-pregnant) with loss of protective upper airway reflexes. This increases the risk of aspiration.

2- Changes of the Epidural and Subarachnoid Spaces:

1- Doses of local anesthetics are decreased about 40% (even in the 1st trimester) for both blocks because:

- **The volume** of both epidural and subarachnoid spaces is **decreased** which allows more cephalad spread of local anesthetics due to dilatation and engorgement of epidural veins. The engorgement of epidural veins occurs due to:
 - the progesterone effect,
 - the aorto-caval compression, and
 - increased intra-thoracic or intra-abdominal pressure by straining.
- **Hyperventilation** occurs due to the effect of progesterone. This decreases PaCO_2 which results in increased renal compensatory HCO_3^- excretion. Therefore, HCO_3^- is decreased causing a **decrease in buffering capacity** which in turn allows local anesthetics to remain as free salts for a longer time resulting in increasing their action.
- **The increased pressure in epidural space** facilitates diffusion of local anesthetics across the dura. This increases local anesthetic concentration in cerebrospinal fluid.

- **Venous congestion at lateral foramina** decreases escape of local anesthetics along the dural sleeves.
- **Exaggerated lumbar lordosis** increases cephalad spread of local anesthetics.
- **Anti-nociceptive effect of pregnancy** is obvious by:
 - increased sensitivity of peripheral nerves to lidocaine,
 - and - depressing effect of progesterone on excitability of nervous tissues.

2- Epidural pressure increases and changes from the negative pressure to positive pressure and increases more during uterine contraction up to 5.9 KPa in the 2nd stage. Therefore, top up doses should be avoided at the time of uterine contractions because this increases the spread. **Cerebrospinal pressure increases** and increases more during uterine contractions up to 6.9 KPa in the 2nd stage.

In sitting position, both pressures increase more causing bulge of the dura which results in:

- Increased risk of cephalad spread of local anesthetics.
- Increased risk of inadvertent dural puncture.

3- Respiratory Changes:

1- The respiratory center is stimulated by progesterone; therefore,

- The minute volume is increased about 50%. This is one of the earliest changes. This explains the faster onset of induction and emergence from anesthesia than in the non-pregnant females.
- Tidal volume, respiratory rate, and PaO_2 increase while PaCO_2 and HCO_3^- decrease by the same level; therefore, **the pH remains normal (7.4).**

2- The diaphragm is elevated by the pregnant uterus. This causes:

- Increased antero-posterior diameter of the chest and increases the thoracic breathing more than the abdominal breathing.
- A 40% decrease in the chest and lung compliance.
- A decrease in the expiratory reserve volume and residual volume which in turn causes a decrease in the functional residual capacity (FRC).

N.B.: There are no changes in - Vital capacity (some recent studies suggest an increase).

- Closing volume.
- Peak expiratory flow rate (PEFR).
- Forced expiratory volume in the first second (FEV_1).
- Total lung capacity.

3- Hypoxemia is common due to:

- Increased O_2 consumption about 20%.
- Decreased FRC about 20%. The closing volume (which is constant) exceeds FRC in 50% of pregnant females in the supine position causing atelectasis.

Therefore, rapid O_2 desaturation during the period of apnea is common which necessitates preoxygenation prior to induction of general anesthesia.

4- Dead space:

- The anatomical dead space is unchanged except in late pregnancy, where it is decreased due to upper airway edema.
- The physiological dead space is decreased.

5- Oxy-hemoglobin dissociation curve:

- It is shifted to the right (i.e., P_{50} is increased from 27 to 30 mm Hg). This increases O_2 delivery to tissues due to increased RBCs 2,3 di-phosphoglycerate.

6- Engorgement of the respiratory mucosa:

- This easily allows upper airway trauma, bleeding, and obstruction; therefore, gentle laryngoscopy, use of small endotracheal tubes (6.5-7 mm ID) and gentle suction are recommended.

4- Cardiovascular Changes:

1- A state of hyperdynamic circulation is present. **Increased heart rate 15%, stroke volume 30%, and cardiac output 45%** are observed with maximum effect at the second trimester.

- During labor, the cardiac output doubles due to expulsive force at the 2nd stage.
- In the immediate post-delivery period, cardiac output increases further due to auto-transfusion of blood contained in the uterus. These are the most dangerous times for mothers with cardiac disease or pre-eclampsia, so regional anesthesia may protect these patients.

2- Vasodilator effect of progesterone causes:

- **Decreased pulmonary vascular resistance** 34%, but no change in pulmonary artery pressure or pulmonary capillary wedge pressure (PCWP) occurs due to increased blood volume and cardiac output.

- **Decreased systemic vascular resistance** 20%; therefore, diastolic blood pressure is also decreased 20%, but a little change in systolic and mean blood pressure occurs due to increased blood volume and cardiac output.

- **Decreased tone in capacitant veins**, but no change in central venous pressure (CVP) due to increased blood volume and cardiac output.

3- Decreased oncotic pressure:

- Because the increase in plasma volume is mainly due to H₂O rather than colloid component, the oncotic pressure - PCWP gradient is decreased significantly. Therefore, a pregnant female is more liable to develop pulmonary edema.

4- Aorto-caval compression (supine hypotension syndrome):

It occurs in 10-20% of pregnant females, after 28 weeks of pregnancy.

a- Compression of the inferior vena cava (IVC):

- It is done by the gravid uterus on lying supine which **decreases venous return**. The latter **decreases cardiac output** and blood pressure causing stimulation of compensatory mechanisms which include:

- Sympathetic stimulation leading to vasoconstriction and increased heart rate.
- Increased venous pressure below the level of IVC obstruction. This diverts venous blood from the lower ½ of the body via paravertebral venous plexus to the azygos vein which drains into the superior vena cava and right heart.

These compensatory mechanisms increase venous return, cardiac output and blood pressure again.

- If the compensatory mechanisms are enough, they maintain blood pressure and no symptoms appear. This is called **concealed caval occlusion**.

- If the compensatory mechanisms are not enough (e.g., during general anesthesia or regional anesthesia), cardiac output and blood pressure decrease and symptoms such as nausea, vomiting, dizziness, anxiety and **fetal hypoxia** (causing fetal acidosis and bradycardia) appear. This is called **revealed caval occlusion**.

b- Compression of the aorta:

- Compression of the aorta is done by the gravid uterus on lying supine. This **decreases the blood pressure** to the lower ½ of the body causing **decrease in utero-placental blood flow** which in turn produces **fetal hypoxia** (causing fetal acidosis and bradycardia).

Therefore, **avoid the supine position after 28th week of pregnancy** by (figure 10-1):

- Lateral uterine displacement (usually to the left side >15 degrees) by:
 - rotating the delivery table to the left,
 - mechanically displacing the uterus to the left in the supine parturient,
 - or ◦ placing a pillow or wedge under the right side of the back and buttock.
- I.v. fluids.
- I.v. ephedrine (if hypotension occurs).

5- Elevation of the venous pressure in the lower limbs increases liability to phlebitis, edema and varicose veins.

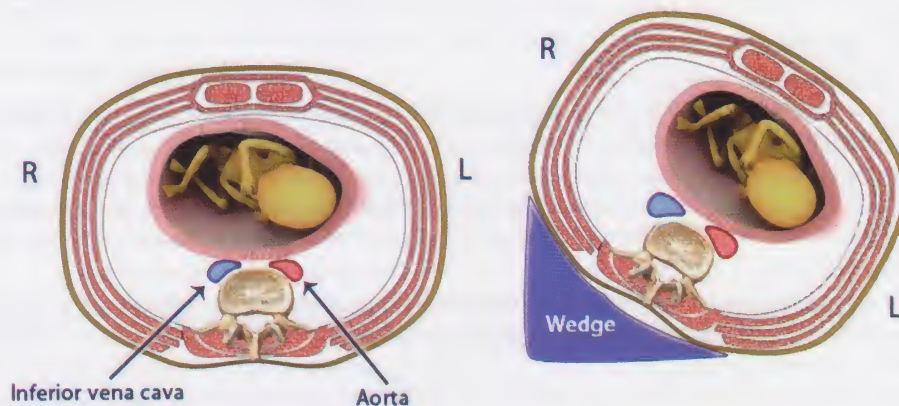


Figure 10-1: Left lateral tilt in a pregnant female

6- Heart auscultation shows:

- Increased S₁ and S₂ splitting.
- Appearance of S₃ in 84% and S₄ in 16%.

- Soft systolic ejection murmur (grade I or II) in 90% which may be due to tricuspid or mitral regurgitation resulting from dilatation of their annuli.
 - Soft early diastolic murmur in 10%.
7. **Chest x-ray** shows an enlarged heart. This occurs mainly due to shifting of the heart upwards by the elevated diaphragm. The heart's size of pregnant females increases only by about 12%.
- 8- **Electrocardiography (ECG)** shows left axis deviation, ST segment depression, and flat or inverted T wave besides sinus tachycardia. This occurs due to shifting of the heart upwards by the elevated diaphragm.
- 9- **Echocardiography** shows normal findings with the following differences:
- An increase in the sizes of the heart chambers: 20% in the right atrial and right ventricular sizes.
15% in the left atrial size.
10% in the left ventricular size.
 - The annuli of pulmonary, tricuspid, and mitral valves dilate progressively which may result in mild valvular regurgitation.
 - Little pericardial effusion.

5- Hematological and Immunological Changes:

- 1- **Increased blood volume** 40% to reach 85-90 mL/kg at term. This occurs due to:
increased plasma volume 45%
and increased red blood cell volume 20%.

This causes a dilutional effect which is **maximal at 32nd week of pregnancy**. This results in **physiological anemia of pregnancy** (i.e., decreased hemoglobin to 12 g% and hematocrit to 36% "about 15 % of the normal values").

This allows the pregnant woman to tolerate blood loss during vaginal delivery (400-500 mL) and cesarean section (800-1000 mL).

2- Cells:

- There is a decreased red blood cell count due to the dilutional effect (i.e., decreased count/L), although red blood cell production is increased.
- There is an increased white blood cell count especially neutrophils due to the estrogen effect.
- There is a slight decrease in the platelet count.

3- Immunity:

- Cell mediated immunity is depressed due to decreased lymphocyte function to allow tolerance of the antigenically foreign placenta. This increases viral and bacterial infection.
- Humoral immunity and immunoglobulins remain normal.

6- Renal Changes:

- Increased renal blood flow, creatinine clearance and glomerular filtration rate about 50% become apparent at 10-15th week of gestation.
- Serum creatinine decreases to 0.5-0.6 mg% (50%) and blood urea nitrogen decreases to 8-9 mg% (50%).
- Renal tubular threshold decreases for glucose causing mild glucosuria (1-10 g/day) and for amino acids causing proteinuria, but less than 300 mg/day.

7- Hepatic Changes:

- No change occurs in hepatic blood flow or hepatic function.
- Serum alkaline phosphatase increases due to its placental secretion.
- Total proteins and serum albumin decrease due to the increased plasma volume i.e., the dilutional effect.
- Serum pseudo-cholinesterase decreases by 30%, but clinically, it does not affect the action of suxamethonium, mivacurium or the ester type of local anesthetics.

8- Gastrointestinal Changes:

Gastro-esophageal reflux increases which predisposes the pregnant females to esophagitis, risk of regurgitation and aspiration. This occurs because:

- The stomach is shifted upward by the gravid uterus resulting in:
 - Incompetent gastro-esophageal physiological sphincter.
 - Increased intragastric pressure > lower esophageal sphincter pressure.
- Progesterone decreases gastric motility and tone of gastro-esophageal sphincter.

- Placental gastrin hormone increases gastric acidity (gastric pH becomes < 2.5 and gastric volume increases >25 mL).
- During labor:
 - administration of narcotics and anticholinergics decreases gastro-esophageal sphincter tone.
 - labor pain and anxiety delay gastric emptying up to 18 hours (gastric emptying is not delayed during pregnancy).

9- Hemostatic Changes:

- There is an **increase in factors I "fibrinogen"** (which changes negative surface charges on red blood cells causing **rouleaux formation** and increases erythrocyte sedimentation rates), **II, V, VII, VIII, IX, X, and XII.**
 - There is a **decrease in factors XI and XIII.**
 - There is an increase in plasminogen inhibitors and a decrease in plasminogen activators causing inhibition of fibrinolysis which results in **increased clot formation and a hypercoagulable state.**
- N.B.:** No change occurs in plasminogen, bleeding time, prothrombin time and partial thromboplastin time.

10. Metabolic Changes:

- There are changes in carbohydrate, fat, and protein metabolism to favor fetal growth.
- Pregnancy is a diabetogenic state where there is a relative insulin resistance due to human chorionic somatomammotropin. The latter increases the level of insulin and causes hyperplasia of pancreatic β cells.
- Hypertrophy of the thyroid gland may occur, causing increased total T3 and T4 due to human chorionic gonadotrophin (hCG). No change in free T3, T4, and thyroid stimulating hormone (TSH) is observed.

11- Hematinics:

1- Iron requirement increases during pregnancy due to:

- Increased maternal red blood cell volume.
- Increased blood loss during delivery.
- Increased placental and fetal needs.
- Subsequent breast feeding.

Routine iron supplementation is not necessary in pregnant females with adequate nutrition and singleton pregnancy due to increased iron absorption.

2- Folate requirement increases during pregnancy:

- Its deficiency causes fetal deformity (neural tube defect), premature labor, and ante-partum hemorrhage; therefore, folate supplementation is required.

3- Vitamin B₁₂ requirement increases during pregnancy:

- Its deficiency causes intrauterine fetal death; therefore, vitamin B₁₂ supplementation is required in strict vegetarians.

12- Utero-Placental Blood Flow (UBF) Changes:

At term UBF is about 500-700 mL/min (50 mL/min in non-pregnant females). Eighty % is directed to the placenta and 20% to the myometrium. It represents 10% of cardiac output approximately.

No autoregulation is present because during pregnancy uterine vessels are maximally dilated and spiral arteries have no smooth muscle layer; therefore, UBF is directly proportionate to uterine perfusion pressure (figure 10-2).

As • Perfusion pressure = forcing pressure which pushes blood to the organ
 - opposing pressure which resists blood to the organ

$$\bullet \text{ Blood flow to an organ} = \frac{\text{Perfusion pressure}}{\text{Vascular resistance}}$$

$$\text{Therefore, UBF} = \frac{\text{Uterine perfusion pressure}}{\text{Uterine vascular resistance}}$$

$$= \frac{\text{Uterine arterial pressure} - \text{Uterine inter-villous pressure}}{\text{Intrinsic resistance of spiral arteries} + \text{Extrinsic resistance (myometrium tone)}}$$

$$= \frac{\text{Uterine arterial pressure} - (\text{Intrauterine pressure} + \text{Uterine venous pressure})}{\text{Intrinsic resistance of spiral arteries} + \text{Extrinsic resistance (myometrium tone)}}$$

Spiral arteries have low resistance because they have no smooth muscle layer.

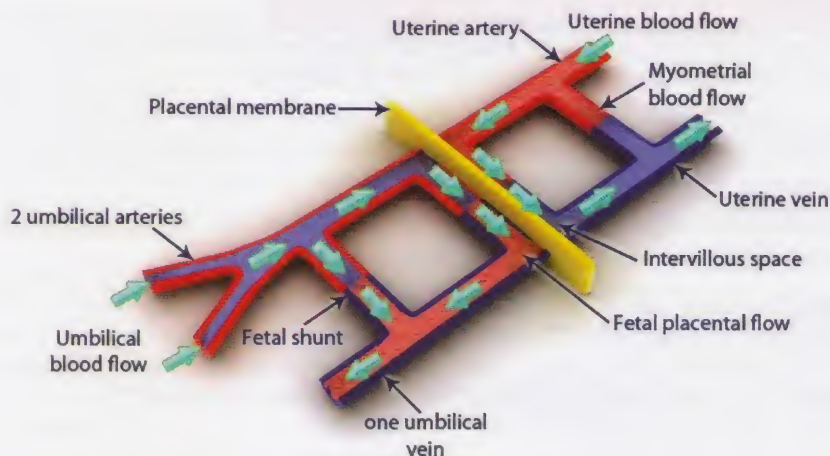


Figure 10-2: Utero-placental circulation

UBF is decreased by:

a- Reduction of the uterine perfusion pressure such as:

- Hypotension e.g., - aorto-caval compression,
- hypovolemia (hemorrhage),
or - sympathetic blockade due to regional anesthesia.

b- Elevation of uterine vascular resistance such as:

- Uterine artery vasoconstriction e.g.,
▫ stress-induced release of endogenous catecholamines during labor,
▫ hypertension and pre-eclampsia,
▫ extreme hypocapnia e.g., $\text{PaCO}_2 < 20$ mm Hg, and
▫ drugs with α adrenergic activity e.g., phenylephrine.

N.B.: Ephedrine has mainly β adrenergic activity; therefore, it is of choice in hypotension with pregnancy.

- Uterine contractions e.g., - during labor.
- during oxytocin infusions.

The normal fetus can tolerate 50% reduction in UBF because there is good circulatory reserve. If UBF is decreased more, fetal hypoxia occurs, which in turn produces fetal acidosis (it is used to test the adequacy of UBF) and bradycardia.

Effect of Anesthetic Agents on UBF:

1- Volatile anesthetics decrease maternal blood pressure which decreases UBF.

2- I.v. anesthetics

- Barbiturates and propofol decrease maternal blood pressure which decreases UBF.
- Ketamine produces no effect on UBF because its vasoconstricting effect is compensated by its increase in maternal blood pressure.

3- Local anesthetics especially lidocaine, if it is unintentionally intravenously injected, uterine vasoconstriction is produced leading to a decrease in UBF.

N.B.: - Spinal and epidural anesthesia have no effect on UBF provided that hypotension is avoided.

- Epidural anesthesia in pre-eclampsia actually increases UBF because it decreases pain and stress which decreases endogenous catecholamines.

- Addition of epinephrine to local anesthetics has no effect on UBF.

Effect of Labor on Maternal Physiology

During intense uterine contractions, there is an increase in the following parameters, over the 3rd trimester values.

- Minute volume is increased 300% which decreases PaCO_2 less than 20 mm Hg.
- O_2 consumption is increased 60%.
- Cardiac output is increased 45%.

Immediately, in the post-delivery period, when intense uterine contractions suddenly stop, inferior vena caval obstruction is released, and auto-transfusion of blood from the placenta to the mother circulation occurs, the cardiac output increases up to 80%. This is the most dangerous time for mothers with cardiac disease or preeclampsia.

Placental Transfer of Anesthetic Agents

Anesthetic agents are transferred mainly by **passive diffusion** through the placenta. The rate of passive diffusion is determined by **Fick's law of diffusion**.

$$\text{Rate of diffusion} = K \frac{A [C_m - C_f]}{D}$$

Where K is diffusion constant of the drug.

C_m is the maternal drug concentration in the venous blood.

C_f is the fetal drug concentration in the umbilical vein.

A is the surface area of placental membrane.

D is the thickness of placental membrane.

Diffusion constant (K) depends on:

1- **Molecular weight**: lower molecular weight increases diffusion (**Graham's law**).

2- **Lipid solubility**: higher lipid solubility increases diffusion.

(Both depend on the type of the drug).

3- **Protein binding**: lower protein binding increases diffusion. It depends on the pH of the maternal blood, for example, acidosis decreases protein binding of local anesthetics.

4- **Degree of ionization**: lower degree of ionization increases diffusion. It depends on the pH of the mother and fetus.

Fetal acidosis (i.e., decreased fetal pH) ionizes the weakly basic drugs such as **local anesthetics and opioids** in the fetal circulation. These drugs cross the placenta in the non-ionized form only. Since an ionized drug can not readily cross the placenta back into the maternal circulation, these drugs will accumulate in the fetal blood against a concentration gradient. This phenomenon is called **ion trapping** e.g. increased lidocaine in fetal blood during fetal stress.

For example:

a- Drugs freely crossing the placenta:

- Almost all i.v. and inhalational anesthetic drugs.
- All opioids.
- Ephedrine, β blockers as labetalol, and esmolol, vasodilators, phenothiazines, anti-histaminics (H_1 and H_2), and metoclopramide.
- Atropine and hyoscine (but not glycopyrrolate because it is a quaternary amine).

b- Drugs poorly crossing the placenta:

- Local anesthetics especially bupivacaine due to its high protein binding.
- Skeletal muscle relaxants except gallamine.

Fetal Affection of Drugs Given to the Mother

Distribution of maternal anesthetic drugs (assessed by the maternal vein concentration) to the placenta and the fetus (assessed by the umbilical vein concentration) and their effect on the neonate depends on many factors:

Maternal Factors:

1- **The amount of the drug reaching the placenta** which depends on:

- the route (i.v., i.m., epidural...).
- the dose.
- the time of administration relative to uterine contractions. Utero-placental blood flow is decreased by uterine contractions; therefore, if i.v. dose is given just before uterine contractions, the amount of the drug reaching the placenta is reduced.
- Time of administration relative to delivery e.g., if pethidine is given to the mother before fetal birth by 3 hours, respiratory depression of the fetus occurs.

2- **Factors affecting placental transfer of drugs** (see above).

Fetal Factors:

1- **The position of the liver in the fetal circulation**: The drugs from the placenta pass via the umbilical veins to the **liver (the first organ in the fetus after the placenta)** where the drugs are metabolized before distribution, decreasing the drug concentration in the fetus.

2- The **relatively high extracellular fluid volume** of the fetus which explains the large volumes of distribution of drugs.

3- The low plasma proteins binding in the fetus: Fetal plasma contains less α_1 -glycoproteins and albumin at term, which affects protein binding of drugs particularly local anesthetics.

4- Maturity of the fetal organs:

- The brain of the fetus is immature, affecting its response to the administered drugs.
- The hepatic function of the neonate is immature e.g., there is no hydroxylating system.
- The renal function of the neonate is immature which decreases renal drug elimination.

Individual Drug Behavior in Neonates: after their administration during labor or cesarean section:

1- Inhalational Anesthetics:

- Although they cross the placenta readily, their concentration in the neonatal plasma is minimal producing minimal nervous system depression as long as the induction-delivery interval is short because of:
 - their metabolism by the fetal liver before reaching the fetal central nervous system,
 - their dilution by drug free blood returning from the lower extremities and pelvic viscera of the fetus via ductus venosus, and
 - the relatively large fetal volume of distribution.
- The maternal plasma concentration is reached in the neonatal plasma after one hour which does not occur during cesarean section.

2- Thiopental:

- Although it very readily crosses the placenta, its concentration in the neonatal plasma is very minimal due to the same reasons of inhalational anesthetics as above.
- The fetal plasma concentration increases and causes neonatal depression in the following conditions:
 - Within 40 min after single maternal exposure to the thiopental as its concentration increases gradually within the fetus.
 - After repeated boluses of thiopental.
 - After high maternal doses such as more than 8 mg/kg.

N.B.: Doses less than 4 mg/kg produce no significant neonatal effects provided that induction-delivery interval is less than 5 min, but at these low doses, slight changes in the neuro-adaptive score occur such as reduction in muscle tone, decreased excitability, and a predominant sleep state in the first day of life.

Doses of 4-7 mg/kg are commonly advocated for induction of general anesthesia because they ensure unconsciousness and decrease the possibility of awareness.

3- Propofol:

- It crosses the placenta very readily with high fetal plasma concentration. Induction doses as low as 2-3 mg/kg and maintenance doses as low as 5 mg/kg/hour cause significant neonatal depression because the neonatal elimination of propofol is slower than that in adults. Propofol is relatively contraindicated in cesarean section except if thiopental is contraindicated.

4- Skeletal Muscle Relaxants:

- As they are quaternary ammonium compounds and fully ionized, they cross the placenta very slowly, making the neonatal plasma concentration low during anesthesia e.g., during succinylcholine boluses or the usual doses of muscle relaxants.
- If the relaxant is administered for a long duration e.g., in the intensive care, neonatal paralysis may occur.

5- Diazepam:

- It crosses the placenta very readily causing respiratory depression, hypotonia, poor thermoregulation, and raised bilirubin concentrations; therefore, it is better to be avoided especially on prolonged maternal administration as in intensive care units.

6- Opioids:

All opioids cross the placenta very readily causing neuro-behavioral and respiratory depression in neonates and decreasing apgar score by variable degrees, depending on the dose and administration-delivery interval.

- **Morphine:** produces more neonatal depression than other agents.
- **Pethidine:** produces maximum neonatal depression within 2-3 hours after i.m. administration and 10-20 minutes after i.v. administration.
- **Fentanyl:** i.v., intrathecal, or epidural administration ($> 200 \mu\text{g}$) produces neonatal depression. Intrathecal fentanyl may cause also sudden fetal bradycardia and uterine hypertonicity.
- **Alfentanil, sufentanil** ($< 30 \mu\text{g}$), and **remifentanil** produce less neonatal depression.

Lactation and Drugs in Obstetric Anesthesia

- Many women wish to nurse their infants immediately after delivery and are encouraged to do so. The anesthesiologists should know if the drugs used for obstetric anesthesia and analgesia are secreted in milk and affect the neonate.
- Transfer of drugs through the breast milk (like transfer through the placenta) depends on:
 - Molecular weight.
 - High lipid solubility.
 - Protein binding.
 - Degree of ionization.

This is besides the immaturity of the liver and kidneys of the neonates.

For example:

1- Opioids:

- **Morphine, fentanyl, and alfentanil** are **safe** due to their high first pass metabolism with inactive metabolites. Although the morphine produces an active metabolite "morphine 6-glucuronide", its level in the infant is too low to affect respiration.

- **Pethidine** produces neonatal neuro-behavioral and respiratory **depression**.

2- Non-steroidal anti-inflammatory drugs:

- **Ketorolac and diclofenac** are **safe**.
- **Aspirin** should be avoided even for a single dose as it may cause **Reye's syndrome** in neonates.

3- Paracetamol, thiopental, propofol, lidocaine and bupivacaine are safe.

- 4- **Diazepam** may produce **floppy infant syndrome** which is characterized by hypotonia, lethargy, poor feeding, hypothermia, and respiratory distress in neonates.

Effects of Anesthetic and Other Relevant Drugs on Uterine Activity and Labor

1- Inhalational Anesthetics:

They produce dose dependent uterine relaxation (< 0.5 - 0.75 MAC has no effect).

2- Regional Anesthesia:

a. **Direct Effects:** In toxic doses, tetanic contractions are produced.

b. **Indirect Effects:**

1. Prolongation of labor:

- **Early in 1st stage:** regional anesthesia is suggested to prolong the early course of labor, but this is very difficult to be confirmed. Actually, it abolishes stress and pain-induced release of endogenous catecholamines which can inhibit coordinated and effective uterine contractions, so it can enhance early progress of labor.

- **2nd stage of labor** can be prolonged because regional anesthesia removes the reflex urge of the parturient to bear down.

2. **Increasing incidence of mid-forceps deliveries:** This is controversial because:

- It removes the reflex urge of the parturient to bear down in 2nd stage.
- It abolishes a reflex increase in endogenous oxytocin from distention of the lower birth canal (Ferguson reflex).
- Relaxation of pelvic musculature interferes with flexion and internal rotation of the fetus which may predispose to persistent occiput posterior presentation.

All these effects can be avoided by:

- using low concentration of local anesthetics for epidural anesthesia to preserve skeletal muscle function or
- withholding perineal doses of local anesthetics until descent and rotation of the fetus have occurred.

3. Effect of fluid loading with the start of epidural block:

Fluid load decreases endogenous oxytocin secretion from the pituitary gland (the same as fluid loading decreases endogenous antidiuretic hormone). This decreases uterine activity transiently.

3- α_1 Receptor Agonists cause uterine contractions e.g., phenylephrine, methoxamine, or metaraminol.

4- Tocolytics: They depress uterine contractions and produce uterine relaxations.

- **β_2 Receptor Agonists:** ritodrine (*Yutopar*), yohimbine, or terbutaline.

N.B.: Epinephrine-containing local anesthetics may produce uterine relaxation.

- **Magnesium:** is also in preeclampsia.
- **Nitroglycerin:** is recently used as a uterine relaxant and tocolytic.
- **Atosiban:** is an oxytocin antagonist used to decrease uterine contractions. It is expensive.
- **Indomethacin (or Indomethacin):**

It is a PG synthetase inhibitor. It is given orally or rectally to inhibit uterine contractions after cervical circlage.

It may cause premature closure of the fetal ductus arteriosus and therefore, should not be used after 32 weeks' gestation.

5- Ecbolics:

- **Syntocinon (Oxytocin):** (*Pitocin or Syntocinon*)

Doses:

- 5 IU i.v. infusion to induce and increase uterine contraction aiming to fasten the duration of normal labor.
- 10-40 IU i.v. infusion to avoid and treat postpartum hemorrhage.

Side effects:

- It may act on some vascular smooth muscles resulting in **hypertension**.
- **Rapid i.v. injection** produces transient **systemic vasodilatation**, hypotension, and reflex tachycardia due to relaxation of vascular smooth muscles. This may produce **fetal distress**.
- **Large doses** may produce **water intoxication** and hyponatremia especially if used **with dextrose solution** due to its antidiuretic hormone action.
- **Methyl Ergonovine (Ergometrine):** (*Methergine*)

Doses: 0.2 -0.5 mg i.m. or i.v. infusion to increase the duration and power of uterine contractions.

Side effects:

- **Rapid i.v. injection** may cause acute **hypertension, cerebro-vascular strokes, pulmonary edema, and coronary vasospasm** due to its vasoconstricting action via its α -adrenergic action. Therefore, it is avoided in pregnancy induced hypertension.
- **Nausea and vomiting** are common.

- **Syntometrine:**

It is a combination of syntocinon 5 units and ergometrine 0.5 mg which is given i.m.

- **Prostaglandins (PGs):**

They include:

- Carboprost (Hemabate):** a **PG F_{2α} analogue**. It is given i.m. or into the myometrium at cesarean section.
- Misoprostol (Vagiprost):** a **PG E₁ analogue**. It is given vaginally, orally, or rectally.
- Dinoprost (Enzaprost-F or Prostin-E2):** a **PG E₂ analogue**. It is given vaginally, orally, or rectally.

Uses:

- To ripen the cervix in induction of labor.
- To contract the uterus after labor and cesarean section and to treat postpartum hemorrhage due to uterine atony.

Side effects: especially with i.v. injection - Bronchospasm.

- Systemic and pulmonary hypertension.
- Nausea, vomiting, and diarrhea.
- Pyrexia and shivering.

N.B.: **Mifepristone:** is a **PG antagonist**. It causes luteolysis and trophoblastic separation. It is given orally and causes headache, dizziness, and gastrointestinal upset.

Physiology of Pain in Labor

The origin, type, and site of labor pain differ according to the stage of labor.

	First Stage of Labor	Second Stage of Labor
Stage	It starts from the onset of regular contractions till complete cervical dilation.	It starts from complete cervical dilation till delivery of the baby.
Origin	<ul style="list-style-type: none"> • Dilation of the cervix. • Contraction of the uterus. • Traction on the round ligament. 	<ul style="list-style-type: none"> • Distention and stretching of the perineum and vagina. • Pressure by the presenting part on bladder, urethra, and rectum.

Type of pain	Visceral pain and is referred to dermatomes supplied by spinal cord segments T10, T11, T12, and L1.	Somatic
Site of pain	Upper abdominal and groin areas	Perineum
Afferent fibers (needed to be blocked)	Fibers from the cervix and uterus travel in nerves that accompany sympathetic nervous system fibers and enter the spinal cord at segments T ₁₀ , T ₁₁ , T ₁₂ , and L ₁ (figure 10-3).	Fibers from the perineum travel via the pudendal nerve to spinal cord segments S ₂ , S ₃ , and S ₄ .

Third Stage of Labor:

It involves delivery of the placenta. It is a painless stage.

During cesarean section:

As the most sensitive layer is the peritoneum; therefore, the block should extend at least up to T₂₋₄ down to S₁₋₄.

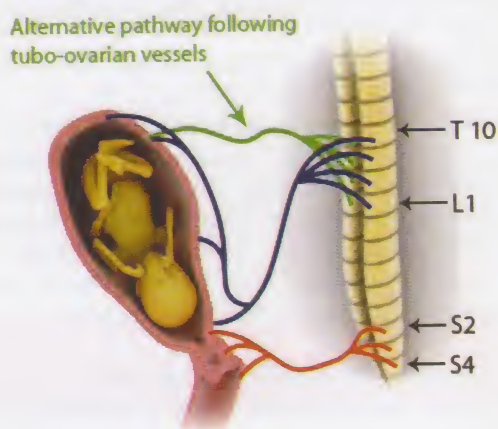


Figure 10-3: Origin of the pain during labor

Sequence of Labor Pain:

1- Unrelieved pain causes **sympathetic stimulation** which produces:

- An increase in cardiac output, blood pressure, and a delay in gastric emptying.
- A decrease in utero-placental blood flow due to:
 - Increased plasma cortisol and catecholamines.
 - Hyperventilation; it produces hypocapnia and respiratory alkalosis causing fetal hypoxia (i.e., acidosis and bradycardia).

2- A long, traumatic, painful labor may lead to an exhausted, frightened and hysterical mother incapable of decision-making and may cause a **post-traumatic stress syndrome**.

Analgesia for Vaginal Delivery

General Considerations for All Pregnant Females in Labor:

- 1- Pre-anesthetic history and examination should be done because pregnant females are liable for anesthesia.
- 2- An 18-gauge or larger i.v. cannula is inserted.
- 3- Patients should be kept NPO and receive i.v. fluids as lactated ringer or dextrose with 0.45% saline to prevent dehydration.

N.B.: **Ketosis** may occur with labor and is not necessarily related to the degree of dehydration.

- 4- Blood samples are sent for typing and screening.

A- Non-Pharmacological Methods

1- Psychological Methods:

- They are taught routinely in antenatal classes such as **breathing techniques (Fernand Lamaz technique)** where a deep breath at the beginning of each contraction followed by rapid shallow breathing for the duration of each contraction is helpful.
- Presence of the father beside the mother usually helps the mother and gives her reassurance.

2- Hypnosis: It involves the patient being in a state of intense concentration, where positive feelings are suggested and reinforced and negative ones played down. This needs a skilled hypnotist and special training sessions before labor to the mother.

3- Acupuncture.

4- Decompression Suit: It is applied to the abdomen. It facilitates labor because it produces good analgesia and shortens the 1st stage.

5- Trans-cutaneous Nerve Stimulation: It depends on the gate theory of pain transmission (as described by Melzack and Wall in 1965). Stimulation must be applied to the dorsal columns of the spinal cord in the mid-thoracic region, above the level of the affected nerve roots i.e., T10. It is effective early in labor, but begins to lose its effect after 5 cm cervical dilatation is reached.

6- Electro-Analgesia.

B- Pharmacological Methods

I) Parenteral Drugs:

1. Opioids:

Disadvantages:

- Maternal: Respiratory depression and delayed gastric emptying.
- Fetal: central nervous and respiratory depression, acidosis, abnormal neurobehavioral examinations, and loss of beat to beat variability (as they cross placenta).

They are easily reversed by naloxone 10 µg/kg into the umbilical cord vein.

For example:

- Pethidine: is the most commonly used opioid.
- Morphine, fentanyl, pentazocineetc can be used (see above).

2. Ketamine:

It is given in an analgesic dose 0.25 mg/kg i.v. It has no effect on utero-placental flow, uterine activity and neonatal status at this dose.

3. Thiopentone: may cause loss of consciousness.

4. Diazepam: It is given in a dose of 5-10 mg i.v. With larger doses > 30 mg, floppy infant syndrome may occur (see above).

II) Inhalational Analgesia:

1. Entonox:

It is the most commonly used in the United Kingdom. It is a premixed N₂O: O₂ (1:1), stored in a gaseous phase in cylinders kept above -7°C.

Analgesia occurs **50 sec after** starting its inhalation. It is not effective if taken with the onset of uterine contractions; therefore, continuous inhalation is preferred. During the 2nd stage of labor, pain is fairly regular, so it is possible to expect contractions and to start inhalation before the expected contraction and continue till pain is maximal followed by bearing down.

Advantages:

- It allows **high inspired O₂** concentration.
- It is **self-administered** by a mask or mouth piece.
- N₂O at that concentration produces **no physiological or biochemical effects**.

Disadvantages:

- It has a **relatively delayed onset**; therefore, it is **not very effective**.
- After delivery, **diffusion hypoxia can occur in the newborn** due to rapid passage of N₂O from blood to the alveoli. O₂ should be given for 30-60 seconds after delivery of the neonate.

2. Subanesthetic Doses of Volatile Agents:

Administration of halothane (< 0.5%) or isoflurane (< 1%), with N₂O allow analgesic action without loss of airway reflexes at these concentrations.

They are used during late 1st stage and 2nd stage of labor by experienced anesthesiologists.

Disadvantages: confusion, excitement or drowsiness is indicative of an overdose which necessitates decreasing the concentration.

III) Local Anesthetic Techniques:

General Considerations:

1- History, explanation, and consent should be taken.

- 2- Adequate equipment for **resuscitation** should be present and available **anesthesiologist** should be ready for intervention at any time.
 - 3- Satisfactory **i.v. line** must be secured before the start.
 - 4- Aorto-caval compression should be avoided by a **left lateral position**.
 - 5- **Arterial blood pressure** should be measured every 5 minutes and more frequently if hypotension occurs.
 - 6- Continuous monitoring of the **fetal heart rate** should occur.
 - 7- Physiology of labor pain should be in mind (see above). Sensory block levels required are as follows: •
- During the **1st stage**: T₁₀ T₁₁ T₁₂, and L₁ should be blocked.
- During the **2nd stage**: the block should be **extended to S₁, S₂, S₃, and S₄**.
 - During **cesarean section**: the block should be **extended to T₂-T₄** (figure 10-4).

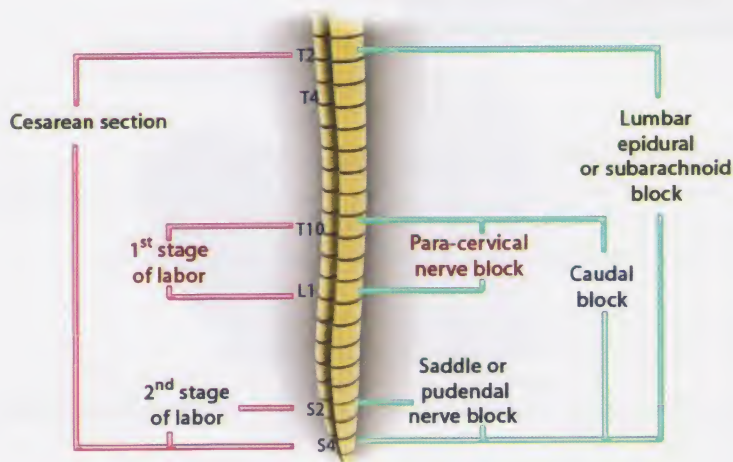


Figure 10-4: Sensory levels blocked during labor and cesarean section

1- Paracervical Nerve Block:

Indications: It is used in the **1st stage of labor** only because it blocks T₁₀-L₁.

Technique: It is usually done by obstetricians. Five mL of 0.25% bupivacaine are injected into the sub-mucosa (superficially) **into each fornix of the vagina lateral to the cervix (at 3.0 clock and 9.0 O'clock)**. It produces anesthesia of the para-cervical plexus (Frankenhauser's ganglia) which contains all the visceral sensory fibers from the uterus, cervix, and upper vagina, but the somatic sensory fibers from the perineum are not blocked; therefore, it is not used in the **2nd stage**.

Disadvantages:

- The site of injection is very close to the uterine arteries; therefore, **uterine vasoconstriction** may occur resulting in a **decrease in the utero-placental blood flow**.
- Very high vascularity is present in the para-cervical area which may cause **increased systemic absorption** and more local anesthetics may be transferred to the fetus, producing high fetal blood levels of local anesthetics which may cause **fetal cardiac toxicity**. **Fetal hypoxia, bradycardia, and acidosis** may occur 2-10 minutes after injections.

Therefore, it is rarely used nowadays and if used, it requires continuous fetal monitoring. It is avoided in patients with fetal distress or insufficient utero-placental circulation.

2- Pudendal Nerve Block:

Indications: It produces block at the level of S₂-S₄; therefore, it is used in the **2nd stage** of labor e.g., episiotomy, outlet forceps, and repair of lacerations.

Technique: It is usually done by obstetricians just before delivery, while the patient is in lithotomy position. Ten mL of 0.5% prilocaine are injected by trans-vaginal approach just **above and behind the palpated ischial spine on each side**. It is usually accompanied by local infiltration of the perineum.

Disadvantages:

- It has with a **low success rate** 60% even with experienced hands.

- If the perineum is infiltrated, **local anesthetic toxicity is very possible** because the total dose of local anesthetics will exceed the maximal dose; therefore, prilocaine 0.5% is the most suitable drug as it has a high toxic dose threshold.

3- Caudal Block:

Indications: It produces block at the level of T₁₀-S₅; therefore, it is used during the 1st and 2nd stages of labor.

Technique: It is discussed later in chapter "Regional and local anesthesia".

If continuous caudal block is required, a catheter can be inserted via a 16-18 gauge i.v. cannula.

Dose: 10-15 mL of 0.25% bupivacaine or 1-1.5% lignocaine are used.

Disadvantages:

- A **lower success rate** than lumbar approach due to anatomic variation, difficulty of the technique, and more pain.
- A higher rate of **infections**.
- **Loss of pelvic muscle tone** during the 1st stage may cause impaired rotation of fetal head which increases instrumental delivery.
- **Puncture of the rectum or fetal head;** therefore, rectal examination should be done before injection.
- **Large doses** of local anesthetics are needed which may increase the risk of toxicity.
- **Complications, like epidural block,** such as dural punctures, intravascular injections...etc.

4- Lumbar Epidural Analgesia:

It is the method of **choice**; with **success rate 80%** (no other technique approaches this level of success).

Indications: It produces block at T₁₀-L₁ for 1st stage,

T₁₀-S₄ for 2nd stage, or

T₂₋₄-S₄ for standard block for **cesarean section**.

It is used **routinely for pain relief** during labor, unless there are contraindications, especially for pregnancy induced hypertension, cardiac and respiratory distress, multiple pregnancy, breech presentation, diabetes mellitus, and **operative labor with full stomach**.

Agents and Doses:

- **Plain bupivacaine 0.125-0.25% concentration** or less with or without opioids as **fentanyl 1-2 µg/mL** is usually used.

- **Epidural loading dose:** 10-20 mL according to the level of analgesia.

- **Epidural maintenance** is performed by one of the following methods:

- **Continuous infusion by a syringe pump:** 8-10 mL/hour.
- **Epidural top ups:** 5-10 mL/hour.

or ◦ **Patient controlled epidural analgesia (PCEA):** 3-5 mL bolus, a 10-15 min lockout time, 4 mL/hour basal rate, and 24mL/hour maximum limit.

This allows sensory block without motor block; therefore, it is called **walking (mobile) epidural anesthesia**. Sensory monitoring should be performed every 30 minutes.

- **Ropivacaine 0.1-0.2%** with or without opioids can be used instead of plain bupivacaine in the same volumes and rates. It produces more differentiation between sensory and motor block allowing greater chance for walking (mobile) epidural anesthesia.

N.B.: Bolus injection (e.g., by top ups or PCEA) may produce more extensive spread of drugs than continuous infusion because bolus doses produce greater injection pressure which makes drug exit from all holes of the multi-holed catheter; while with continuous infusion, drug exits almost exclusively from the most proximal hole. Therefore, PCEA produces better analgesia with less drug consumption than continuous epidural infusion.

Timing:

An epidural block can be performed early in labor when patients request analgesia and should not be withheld simply because cervical dilatation has not been achieved.

The most common timing in **primi-gravida** when the cervix is dilated 5-6 cm.

and in **multi-gravida**, is when the cervix is dilated 3-4 cm.

Techniques, Complications, and Contraindications: see later chapter "Regional and local anesthesia".

Patient Controlled Epidural Analgesia (PCEA) is discussed in more details in chapter of "Pain Management".

5- Subarachnoid (Spinal, Intrathecal) Analgesia:

Indications: It produces block at S₁-S₅ by the **saddle block** for the 2nd stage.

and T₁₀-S₅ by the standard block for cesarean section.

Although it blocks T₁₀-S₅, it is not suitable for the 1st stage of labor due to the short duration of the block; therefore, it is given just before delivery in the 2nd stage.

Technique: differs from that in non-pregnant patients in the following:

- Smaller doses of local anesthetics are used according to the patient's height; 1.5-2.6 mL 0.5% hyperbaric bupivacaine or ropivacaine, with or without fentanyl 10-25 µg or sufentanil 3-10 µg) are usually used.
- Spinal headache is more common, so fine 25-gauge needles should be used.
- Spinal hypotension is more common, so close monitoring of blood pressure is needed.
- Spreading of the drug takes place and so the level of the block is less predictable.
- The technique is more difficult due to exaggerated lumbar lordosis that accompanies pregnancy.

Continuous spinal analgesia by 28 gauge **micro-catheter** is tried, but it may cause cauda equina syndrome especially with 5% lidocaine. Some anesthesiologists use spinal **macro-catheters** (standard epidural catheters placed in the subarachnoid space following an intentional "wet tap") and thread the catheter 3-4 cm within the intrathecal space. Catheter placement can be tested by aspiration of cerebrospinal fluid. The main disadvantage is post-spinal headache.

6- Combined Spinal-Epidural (CSE) Analgesia:

Advantages: It has the combined value of:

- **Rapid onset** and intense sensory anesthesia of subarachnoid block; therefore, it can be used in late labor.
- Possibility of **extending the block** of the epidural catheter; therefore, it can be used in early labor.

Technique:

It is discussed in the chapter of "Regional & Local Anesthesia".

Agents and Doses:

- **Intrathecal injection** is performed at first: 1-2 mL 0.25% bupivacaine or 0.2% ropivacaine with fentanyl 5-25 µg/mL.
- Epidural anesthesia is secondly performed as follows:

When the spinal anesthesia starts to decrease and the first booster is required (usually 60-90 minutes after the spinal injection), an epidural test dose is performed followed by **epidural top up and infusion or PCEA** as above doses, volumes, and rates.

Disadvantages:

- It has the disadvantages of both the spinal and epidural block, but the actual incidence of post-dural puncture headache is less than with epidural alone because the spinal needle may be used to verify the correct position of the epidural needle when loss of resistance is not sure.
- Subarachnoid spread of epidurally administered drugs may occur producing higher level of block.
- Subarachnoid migration of the epidural catheter may occur, but it is very rare.

N.B.: Epidural or Intrathecal Opioid Alone:

Advantages:

1- **Sympathetic block and hypotension do not occur**; therefore, it is useful in patients with hypovolemia, aortic stenosis, pulmonary hypertension, and right-to-left shunts.

2- **Motor block does not occur**; therefore, it preserves the ability of the mother to push during the 2nd stage, but there is a lack of perineal relaxations.

3- **Sensory block** is weak; therefore, mothers can feel contractions and know when to push, but it causes weak analgesia.

4- **Local anesthetic toxicity does not occur.**

Pharmacokinetics, Doses, Disadvantages, and Side Effects:

They are discussed in chapter of "Pain management".

Uterine hyper-stimulation (uterine hypertonicity) and **fetal bradycardia** may occur after intrathecal fentanyl, but recent studies have failed to prove this.

Q: What are the new techniques for labor analgesia?

A: 1- Walking (mobile) epidural anesthesia.

2- Continuous epidural analgesia (by local anesthetics and opioids).

3- Patient controlled epidural analgesia.

4- Continuous spinal analgesia.

5- Combined spinal-epidural analgesia.

6- Epidural or spinal opioid alone.

7- The usage of new local anesthetic drugs as ropivacaine or levo-bupivacaine to decrease cardiac toxicity.

IV) General Anesthesia:

Indication: It is used in vaginal delivery only if one of the following occurs:

- There is a need for **uterine relaxation** e.g., intrauterine manipulation, external cephalic version and extraction, manual removal of retained placenta, replacement of inverted uterus, and breech extraction.
- There are **contraindications to regional anesthesia** and other methods are inadequate.
- If **acute fetal distress** occurs during 2nd stage of labor and operative vaginal delivery is indicated urgently.

Techniques:

- **Left uterine displacement** should be performed by placing a wedge under the right hip.
- **Preoxygenation** for 3-5 minutes is mandatory while applying monitors to the patient.
- **Rapid sequence-crush induction and intubation with cricoid pressure and awake extubation are mandatory** because all pregnant women are at risk of aspiration.

N.B.: Role of Anesthesia in External Cephalic Version:

- It is a method by which manual external pressure is applied to the maternal abdomen to change the position of a fetus from a breech to cephalic presentation.
- Anesthesiologists can increase the success rate of external cephalic version by allowing relaxation of the abdominal wall muscles. This can be performed by **either general anesthesia or neuraxial anesthesia** (epidural, intrathecal, or combined).
- **Tocolytics** are mandatory and helpful in performing a successful external cephalic version.

Anesthesia for Cesarean Section (CS)

The origin of the procedure termed cesarean section predates the Roman Emperor Julius Cesar (100 BC), whose namesake is often involved, although most likely he has not been not born in that way. Jacques Guillimeanu, in his book of midwifery in 1589, is the first person of record to use the word "Cesarean" in connection with "section"; however, because their Latin equivalents (Caesaru and seco) both imply cutting, cesarean "birth" or "delivery" may be the most appropriate description.

Cesarean section represents 25-30% of deliveries nowadays.

I) Regional Anesthesia:

It is more preferred for cesarean section because the risk of mortality is 16.7 times greater with general versus regional anesthesia.

Advantages:

- It **avoids** the risk of **aspiration** of gastric contents.
- **Blood loss** is usually **halved** (compared to cesarean section with general anesthesia).
- It **avoids neonatal depression** by general anesthetic drugs especially a compromised fetus.
- It allows **early maternal-infant bonding** and breast feeding.
- It allows **postoperative analgesia**.

Techniques:

From T₂-T₄ to S₄ is **needed** to be blocked during cesarean section. This can be achieved by one of the following techniques:

- Lumbar epidural anesthesia.
- Lumbar subarachnoid (spinal) anesthesia.
- Combined spinal-epidural anesthesia.

A) Lumbar Epidural Block:

Advantages:

- The advantages of regional anesthesia (mentioned above).
- Opposite to disadvantages of subarachnoid block (see below).

Disadvantages:

- It is time consuming and with a **delayed onset** (45 min versus 10 min in subarachnoid block); therefore, it is unsuitable for emergency cesarean section.
- **More local anesthetics** are used which increase the risk of toxicity and fetal effects especially in premature ones.
- It is relatively **more difficult** than subarachnoid block without positive end point i.e., cerebrospinal fluid detection in the subarachnoid block.
- **There is more patient discomfort** on performance of the block.

Agents and Doses:

• **Plain bupivacaine 0.5% concentration** with or without opioids as **fentanyl 1-2 µg/mL** is usually used. It produces complete anesthesia within 45 min.

- **Epidural loading dose: 15-20 mL** according to the level of analgesia.

- **Epidural maintenance** is done to provide analgesia by continuous infusion, epidural top ups, or patient controlled analgesia as mentioned above with analgesia for vaginal delivery (see above). This allows sensory block without motor block postoperatively, to allow early mobilization of the patient.

• **Lidocaine 2% concentration with 1: 200 000 adrenaline**, with or without opioids can be used.

Recently, new local anesthetic drugs are used such as levo-bupivacaine and ropivacaine, during cesarean section, to decrease the cardiac toxicity. Some other drugs are added such as neostigmine and clonidine to augment the block.

Technique and Complications: are discussed in the chapter of "Regional and local anesthesia".

B) Subarachnoid (Spinal, Intrathecal) Block:**Advantages:**

- The advantages of regional anesthesia (mentioned above)
- Opposite to disadvantages of epidural block (see above).

Disadvantages:

- **Hypotension:** is more severe and more common than with epidural block.
- **Postoperative headache** is more common.
- **The level of anesthesia is less controllable.**
- **No postoperative analgesia** is allowed because there is no possibility of top up doses except if continuous spinal anesthesia is used.

Agents and Doses: The dose is chosen according to patient's height.

- If she is < 155 cm, give 1.8 mL hyperbaric bupivacaine.
- If she is 155- 170 cm, give 2.2 mL hyperbaric bupivacaine.
- If she is > 170 cm, give 2.6 mL hyperbaric bupivacaine.

Fentanyl 10-25 µg or sufentanil 3-10 µg are sometimes added.

Technique and Complications: are discussed in the chapter of "Regional and local anesthesia".

C) Combined Spinal-Epidural Anesthesia

Technique: is similar to that used during normal vaginal delivery.

Agents and Doses:

Intrathecal injection: is similar to spinal anesthesia as above. This is followed by **epidural top up or infusion or PCEA** as above doses, volumes, and rates.

II) General Anesthesia:**Indications:**

- **In emergency cesarean section** for example, peri-mortem cesarean section, fetal distress, or expected hemorrhage in placenta previa (without epidural catheter inserted earlier).
- **Presence of contraindications for regional anesthesia** for examples, patient refusal, back sepsis, coagulopathy ...etc.

A Suggested Technique:

- Preoperative visit and explanation are mandatory as usual.
- Premedications: ◦ **Antacids (in emergency cases) or H₂ antihistaminic (in elective surgery).**
 - **Metoclopramide.**
 - **Glycopyrrolate** (instead of atropine) as anticholinergic and antisialagogue.
- **Left uterine displacement** should be maintained by a wedge under the right hip.
- **Preoxygenation** with 100% O₂ is done for 3-5 min while monitors are applied in emergency cesarean section. Adequate O₂ can be achieved rapidly by 4 maximal breaths with 100% O₂.
- The patient is prepared and draped for surgery.
- When the surgeons are ready, **rapid-sequence crash induction is done with cricoid pressure** performed by a skilled assistant as soon as consciousness is lost by:
 - Thiopentone 5-7 mg/kg (it is a relatively larger dose to decrease possibility of awareness). It is replaced by ketamine 1 mg/kg in hypovolemic patients.
 - Succinylcholine 1.5 mg/kg.
- Surgery is begun only after proper placement of cuffed endotracheal tube size 7.0-7.5.
- Anesthesia is maintained by:

- N₂O: O₂ (5:5).
 - A low concentration of volatile agents (up to halothane 0.5% - isoflurane 0.75% - enflurane 1%). This low concentration ensures amnesia without producing excessive uterine relaxation.
 - Short or intermediate muscle relaxant e.g., atracurium, cis-atracurium, or vecuronium and mechanical ventilation which is adjusted to achieve endtidal CO₂ of 30 mm Hg.
 - After delivery of the baby:
 - The inspired O₂ can be decreased to N₂O: O₂ (6: 4).
 - I.v. opioid is given while the volatile agent is continued at appropriate low concentration to decrease the risk of awareness.
 - Oxytocin infusion 10-20 IU/L is given.
- If the uterus does not contract readily,
- stop volatile agents and increase N₂O: O₂ (7: 3) while opioids are given.
 - methergine 0.2 mg i.m/iv infusion is given.
 - a prostaglandin analogue is given intra-vaginally or rectally as above.
- An attempt to aspirate gastric contents can be made by an oral gastric tube to decrease the risk of aspiration on emergence.
 - Blood loss should be monitored. The usual blood loss during cesarean section is about 800-1000 mL. Cross-matched blood should be available, is but rarely used.
 - On emergence from anesthesia:
 - The muscle relaxant is reversed,
 - the gastric tube is removed if used,
 - and - **awake extubation** is performed.

Risks of Anesthesia for Cesarean Section

There are special risks associated with cesarean section, especially with emergency cesarean section, which discriminate the cesarean section from other types of surgeries. These risks include: • Increased incidence of difficult and failed intubation.

- Increased incidence of inhalation of gastric contents.
- Increased incidence of awareness during general anesthesia.
- Effects of anesthetic agents on the fetus.

I) Difficult (Failed) Intubation

Incidence: of failed intubation in obstetric patients is **10 times** that in the general surgical population. The causes of the increased incidence in obstetric patients are:

- **Laryngeal and airway edema** especially in pregnancy induced hypertension.
- **Large breasts** which act as obstacles to the laryngoscope handle especially in short necked patients.

Risks: Failed intubation carries many risks to the obstetric patients such as:

- Rapid occurrence of **severe hypoxia** which may cause arrest.
- Increased risk of regurgitation and vomiting which may cause aspiration.

Precautions before Attempting Intubation:

- 1- **Pre-anesthetic assessment** of the airway should be carefully established.
- 2- Obtain **optimal laryngoscopic intubation attempts**.
- 3- **All equipment** required for difficult intubation should be available such as:
 - A 2nd laryngoscope with different blade sizes.
 - Different tube sizes, Magill forceps, oral, nasal airways, and laryngeal masks.
 - Introducers, stylets, and bougies.
 - Esophageal obturator and combi-tube.
 - Fiberoptic bronchoscope.
 - Crico-thyroidotomy sets and mini-tracheostomy sets.

For more details, see chapter of "Airway management".

Failed Intubation Drill:

Early decision to apply the protocol of failed intubation drill is very important (figure 10-5).

II) Inhalation of Gastric Contents

Incidence: of inhalation of gastric contents in obstetric patients undergoing cesarean section under general anesthesia is **4 times** that in the general surgical population. The causes of the increased incidence in obstetric patients are discussed in more details in the physiological changes during pregnancy (see above).

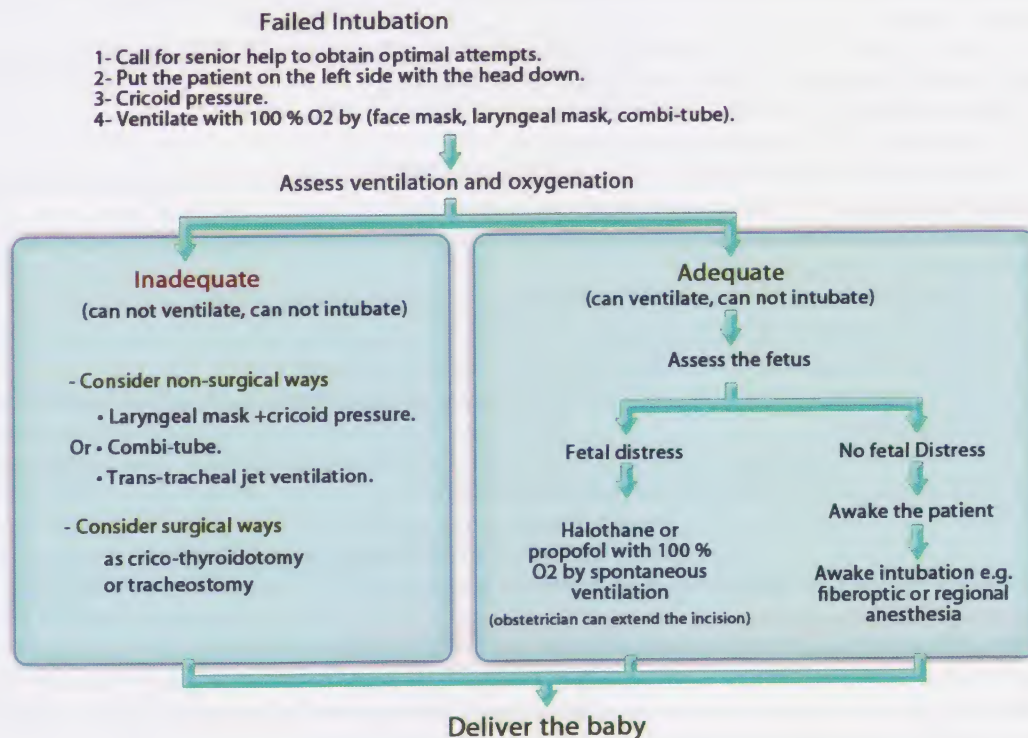


Figure 10-5: Failed intubation algorithm

Risks: Aspiration pneumonia may occur especially if the gastric pH is < 2.5, and the gastric volume is > 25 mL.

Preventive and Prophylactic Measures:

1- Reduction of gastric volume by:

- Maintaining NPO "Nill per os" during labor.
- Insertion of a large gastric tube which has to be withdrawn before induction of general anesthesia.
- Administration of drugs: They do not decrease the already present gastric volume.
 - Metoclopramide 10 mg i.v/i.m 1-2 hours before induction.
 - Cimetidine 300 mg i.v/i.m 1-2 hours before induction.
 - Ranitidine 50 mg i.v or 150 mg i.m 1-2 hours before induction.

2- Reduction of gastric acidity by:

- **Antacids:** They neutralize the existing acids, but increase the gastric volume such as 0.3 M solution of sodium citrate 15-30 mL orally, 15-30 min before induction.

N.B.: Non-particulate antacids (Na citrate or Na bicarbonate) are better than particulate antacids (aluminum or magnesium hydroxide) as the latter mixes poorly with gastric contents and if aspirated, it produces pneumonitis.

- **H₂ receptor antagonists:** They increase the pH up to 5, but do not affect the already existing pH such as cimetidine or ranitidine.

3- Prevention of regurgitation by:

- Increasing lower esophageal sphincter tone by:
 - Metoclopramide.
 - Avoiding diazepam, opioids, and atropine.
- Avoiding increased intragastric pressure by:
 - Avoiding positive pressure ventilation before intubation.
 - Administering de-fasciculating dose of a non-depolarizing muscle relaxant, but recent studies showed that suxamethonium can protect against aspiration and regurgitation.

4- Prevention of inhalation (if regurgitation occurs) by:

- Application of cricoid pressure (Sellick's maneuver).

- Performing rapid sequence (crash) induction in lateral position.
- Presence of a powerful suction.
- Using a cuffed endotracheal tube.

4- Be aware of difficult intubation.

5- Regional anesthesia should be preferred as much as possible.

6- Awake extubation should be performed.

Diagnosis and management of aspiration: "See anesthetic problems"

See the chapter of "Anesthetic problems".

III) Awareness during General Anesthesia

Incidence: of awareness in obstetric patients undergoing cesarean section is 2-26%. The cause of the increased incidence in obstetric patients is the use of low doses of anesthetic drugs especially before delivery of the baby to avoid uterine relaxation.

Risks: Awareness may be auditory, or tactile with/without appreciation of pain.

- Intraoperative sympathetic stimulation decreases utero-placental blood flow.
- Postoperative psychic trauma and dreams.

Preventive Measures:

- Increasing the induction dose of thiopental to 5-7 mg/kg.
- Adding halothane 0.5 % to N₂O: O₂ (5: 5) before delivery.
- Adding opioids and increasing N₂O: O₂ (6: 4) immediately after cord clamping.

For Other Measures, Monitoring, and More Details about awareness during general anesthesia; see the chapter of "Anesthetic problems".

IV) Effect of Anesthesia on the Fetus

1- Hazards of Excessive Maternal Hyperventilation:

It usually occurs due to unrelieved pain, mechanical or manual ventilation and results in hypocapnia (PaCO₂ < 20 mm Hg). This causes:

- Vasoconstriction of utero-placental vessels which decreases utero-placental blood flow.
- Respiratory alkalosis which shifts oxy-hemoglobin dissociation curve to the left and decreases O₂ delivery to the fetus.

Both cause fetal hypoxia which results in fetal acidosis and bradycardia.

2- Hazards of Anesthetic Drugs:

- Effect of anesthetic agents on utero-placental blood flow.
- Fetal affection of drugs given to the mother.

Both are discussed above.

3- Induction-Delivery Interval:

• During general anesthesia, the concentration of anesthetic drugs increases progressively in fetal circulation. On prolongation of induction-delivery interval, neonatal depression may occur.

The optimal induction-delivery time is 10-20 min (up to 30 min).

- The uterine-delivery interval (i.e., the time from the uterine incision to delivery) is more important.

After 90 sec, fetal asphyxia and acidosis begin due to:

- Partial placental separation.
- Impaired placenta blood flow.
- Premature fetal respiratory efforts causing aspiration of liquor.

N.B.: The urgent nature of obstetric operations added to certain obstetric complications (e.g., preeclampsia, breech presentation, and fetal distress....etc.), add to the risk of general anesthesia in obstetrics and emergency cesarean section.

Q: Discuss the anesthetic management of emergency cesarean section?

A: Discuss: • General anesthesia is used instead of epidural anesthesia.

- Risks of anesthesia of cesarean section are increased e.g., failed intubation, aspiration...etc.
- Causes of emergency cesarean section e.g., eclampsia, rupture uterus, or fetal distress.

Q: Discuss the anesthetic management of high risk cesarean section?

A: Discuss: • Risks of anesthesia of cesarean section are increased e.g., failed intubation, aspiration...etc.

- Complicated high risk cesarean section.

Anesthesia for High Risk (Complicated) Obstetrics

I) Pre-eclampsia and Eclampsia

Definition:

Pre-eclampsia: occurs after the 20th week of pregnancy (i.e., the 2nd half) and it is triad of:

- **Hypertension:** It is diagnosed if one of the following measures occurs:
 - The arterial blood pressure is $\geq 140/90$ or mean >105 mm Hg in a previously normotensive woman.
 - The mean blood pressure is increased > 20 mm Hg above the baseline in a previously hypertensive patient.
- Increased systolic blood pressure > 30 mm Hg above the baseline
or - Increased diastolic blood pressure > 15 mmHg above the baseline

- **Proteinuria:** It is diagnosed if it is > 300 mg/day.
 - **Generalized edema:** especially if associated with a recent rapid weight gain.
- Eclampsia:** occurs in the pre-, intra-, or postpartum period (up to 48 hours). It is a severe form of the disease with generalized grand mal (tonic-clonic) **convulsions** associated with:
- 10% maternal mortality due to congestive heart failure or intracerebral hemorrhage.
 - 10% fetal mortality due to respiratory distress, aspiration of meconium, or prematurity.

Risk Factors of Preeclampsia:

a- Hypertensive Diseases:

- Previous preeclampsia.
- History of chronic hypertension.
- Increased pulse pressure during the first trimester.
- Systolic hypertension during early pregnancy.
- Family history of hypertension during pregnancy.

d- Obstetric Factors:

- Primigravidas (14-20%) compared to in multigravidas (6%).
- African-American races.
- Age older than 40 years.
- Increased trophoblastic mass (e.g., multiple gestation, molar pregnancy).
- Large for gestational age fetus.
- Diabetes.
- Polyhydramnios, particularly in young primigravidas.
- Angiotensinogen gene T235.
- History of smoking.
- Obesity.
- Erythroblastosis fetalis.

c- Coexisting Vascular and Endothelial Diseases:

- Chronic renal diseases.
- Protein S deficiency.
- Circulating anticardiolipin antibodies.
- Lupus erythematosus.
- Activated protein C resistance.

Classification of Hypertension with Pregnancy

by American College of Obstetricians and Gynecologists.

1- Pregnancy induced hypertension (PIH), (formerly known as toxemia of pregnancy): Its incidence is 6-8% of pregnant females. It includes:

- Pre-eclampsia and eclampsia (proteinuric hypertension): mild and severe.
- Gestational hypertension (non-proteinuric hypertension).

2- Coincidental hypertension: chronic hypertension preceding pregnancy.

3- Chronic hypertension with superimposed PIH.

Etiology:

There are many heterogeneous causes of both maternal and placental origin.

a- Immunological Factors: It is the most accepted.

- The contents of seminal fluids as **spermatozoa** may cause antibody formation or produce prostaglandins that cause uterine vasoconstriction.
- Presence of an abnormal maternal-fetal antigen-antibody reaction as the **fetus** has 50% of his genome from the father.

b- Genetic Factor:

Familial tendency towards pre-eclampsia exists in some populations, and it may result from recessive genetic inheritance.

c- Calcium:

In pre-eclampsia, intracellular free Ca^{++} increases (more than in normal pregnancy).

d- Platelet Factor:

In mild pre-eclampsia, serotonin (5-HT) released from aggregating platelets, interacts with endothelial 5-HT₁ receptors, resulting in the release of prostacyclin, nitric oxide (NO), and angiotensin II (causing increase of blood pressure). This improves the utero-placental perfusion.

In early onset severe pre-eclampsia, damaged utero-placental vessels cannot respond to 5-HT effects. Instead, serotonin interacts with 5-HT₂ receptors on vascular smooth muscle cells, inducing vasoconstriction, and 5-HT₂ receptors on platelets, inducing more platelets aggregation.

e- Coagulation:

In pre-eclampsia, there is increased tendency towards thrombo-embolism due to alteration in the plasma ratio between von Willebrand factor and factor VIII coagulant activity.

f- Fatty Acid Metabolism:

In pre-eclampsia, there is increased hepatic uptake of free fatty acids and hyper-triglyceridemia.

Pathology:

In pre-eclampsia, an unknown cause (mostly immunological) causes:

- Prostacyclin (PGI₂) and NO deficiency in mother and feto-maternal tissues.
 - Thromboxane A₂ (TxA₂), serotonin, endothelin, and angiotensin II overproduction in the placenta.
- These cause vasoconstriction, increased platelet aggregation, and decreased utero-placental blood flow.

This leads to **uterine ischemia** which in turn causes:

- Release of **thrombo-plastic materials** which are deposited in renal glomeruli producing **proteinuria**.
- Release of **uterine renin** which stimulates angiotensin system causing more vasoconstriction, **hypertension and edema**.

Pathophysiological Changes (Complications):

Preeclampsia/eclampsia is the **third leading cause of maternal mortality**, and accounts for nearly 20% of pregnancy-related maternal deaths. Most of the complications are due to generalized vasoconstriction.

1- Hematological Changes:

- Decreased blood volume especially plasma resulting in hemoconcentration.
- Platelet activation, thrombocytopenia, and thromboasthenia.
- Disseminated intravascular coagulopathy (DIC).

2- Cerebral Changes:

- Increased central nervous irritability causing **hyper-reflexia up to fits** in eclampsia.
- Increased **intracranial pressure** and **cerebral edema** exaggerated by hypoxia, hypercapnia and acidosis.
- In severe cases, **coma** occurs without eclampsia.
- **Cerebral hemorrhage** is responsible for 30-40% of causes of death in preeclampsia.

3- Respiratory Changes:

- Upper airway and laryngeal **edema**.
- O₂-Hb dissociation curve is **shifted to the left** decreasing O₂ delivery to the fetus.

4- Cardiovascular Changes:

- **Hypertension** with increased systemic vascular resistance.
- **Hyperdynamic state**
- **Left ventricular failure and pulmonary edema** due to decreased colloid oncotic pressure and increased vascular permeability.

5- Ophthalmic Changes:

- Retinal artery spasm.
- Photophobia, diplopia, and visual disturbances.
- In severe cases, bilateral **retinal detachments** due to retinal edema occur causing blindness.

6- Renal Changes: Vasoconstriction decreases renal blood flow, which results in:

- Damaged glomeruli, with consequent decreased **glomerular filtration rate** (i.e., oliguric renal failure) and **proteinuria**.

7- Hepatic Changes:

- **Hepato-cellular damage** resulting in elevated liver enzymes.
- **Sub-capsular hematoma** or liver rupture.
- **Hemolysis** producing jaundice.
- **HELLP Syndrome:**

It is a **severe** form of preeclampsia which may occur ante- or postpartum. It occurs in 20% of patients with severe preeclampsia. It consists of:

Hemolysis: Peripheral blood smear shows micro-angiopathic hemolytic anemia because the red blood cells pass through damaged small vasoconstricted vessels. The smear shows burr cells (crenated, distorted red blood cells with spiny projections along their periphery), schistocytes (small irregular shaped red blood cell fragments), and polychromasia.

Serum bilirubin level is increased especially indirect. Prothrombin time, partial thromboplastin time, and fibrinogen are normal in 96% of patients.

Elevated Liver enzymes: Serum amino-transferases (aspartate amino-transferase "AST" and alanine amino-transferase "ALT") are increased.

Blood urea nitrogen and s. creatinine are also increased in 50% of cases.

Low Platelet count ($< 100\,000/\text{mm}^3$)

- Clinical picture:

- Malaise, nausea, vomiting, jaundice, and epigastric pain.
- Generalized edema, and hypertension.
- Cerebral edema and headache.
- There is increased risk of complications such as DIC, placenta abruption, pleural effusion, acute renal failure and wound infection.
- Maternal mortality is about 1-2%.

- Once diagnosis is established;

- Rapid delivery is indicated.
- Platelet transfusion (if $< 20\,000/\text{mm}^3$).
- Packed red blood cells (if with postpartum hemorrhage).
- Dexamethasone 10 mg/12 hours i.v. improves and increases platelet count, but does not affect outcome.

8- Utero-Placental Changes:

- Uterus: - **Hyperactive** painful contractions.
 - Increased sensitivity to oxytocin.
 - **Couvelaire uterus** (intra-myometrial hemorrhage).
- Placenta: - **Premature aging and infarctions.**
 - Fibrin and calcification deposits.
 - **Abruption** (premature separation of the placenta).
- Fetus: - **Premature labor** is common.
 - **Intrauterine growth retardation** or small for gestational age. There is increased incidence of respiratory distress, aspiration of meconium and increased sensitivity to depression by anesthetic drugs.

Degrees of Preeclampsia:

It is classified into **mild and severe.**

Severe preeclampsia is associated with one of the following criteria:

- **Blood pressure** $> 160/110$.
- **Severe proteinuria** > 2 gram/day.
- **Severe generalized edema.**

With end-organ involvement such as:

- Hematological: - Micro-angiopathic hemolytic anemia.
 - Thrombocytopenia.
- Nervous: - Exaggerated hyperreflexia.
 - Cerebral edema and headache.
 - Fits with eclampsia.
- Cardiovascular: - Congestive heart failure and pulmonary edema.
- Visual: - Marked disturbances.
- Renal: - Oliguria ($< 500\text{ mL}/24$ hours).
 - Serum creatinine $> 1.6\text{ mg\%}$ and blood urea nitrogen $> 20\text{ mg\%}$.
- Hepatic: - Elevated ALT and AST with hepatocellular dysfunction.
- Fetal: - Growth retardation.

N.B.: Supine pressor response:

It is a test that predicts the clinical course of mild pre-eclampsia. It is simple and non-invasive.

Diastolic blood pressure is measured while the patient is in the **lateral** recumbent position and then the increase in diastolic blood pressure, while the patient is in the **supine** position, is measured. The test is done twice to obtain the mean change in diastolic blood pressure.

- If the diastolic blood pressure changes are > 30 mm Hg, patients are prone to get **severe** preeclampsia.
- If the diastolic blood pressure changes are **20-29** mm Hg, patients are prone to get **mild** preeclampsia.
- If the diastolic BP changes are < 20 mm Hg, patients are not prone to get preeclampsia i.e., it is a negative test.

Differential Diagnosis:

- 1- Other causes of hypertension with pregnancy (see before).
- 2- Other causes of proteinuria as urinary tract infection or chronic renal diseases.
- 3- Acute fatty liver of pregnancy.
- 4- Amniotic fluid embolism.
- 5- Placental abruption associated with coagulopathy.

Treatment of Preeclampsia and Eclampsia:

The definitive treatment in severe preeclampsia is **delivery of the fetus and placenta**. The disease resolves within 48 hours after delivery. In rare cases, when the mother is stable on antihypertensive drugs and the fetus is very immature, delivery can be delayed.

1- Improvement of Oxygenation: is obtained by supplying O_2 .

2- Improvement of Circulation: to vital organs as the uterus, placenta and kidney by:

- Keeping the patient in the **left lateral position** to avoid aorto-caval syndrome.
- **Antihypertensive drugs** are used if systolic blood pressure is > 180 mm Hg or diastolic blood pressure is > 110 mm Hg.

The aim: To reach a blood pressure of 150/100 and not less to allow adequate organ perfusion. This is obtained by one of the following drugs:

- **Hydralazine** (the most common).
- **Labetalol** (the 2nd common).
- Nitroglycerine.
- Ca^{++} channel blockers.
- Nitroprusside, but on prolonged use, fetal cyanide toxicity may occur because the liver of the fetus is still immature; therefore, it is better avoided.

Invasive blood pressure is essential if continuous infusion is given.

3- Improvement of Intravascular Volume: guided with central venous pressure or urine output. This is achieved by:

- **Isotonic crystalloids** e.g., lactated ringer till the urine output reaches 30 mL/hour.
- **Colloids** e.g., 5% albumin to correct the decreased colloidal pressure.
- **Blood transfusion** if hematocrit becomes $< 27\%$.

N.B.: Avoid D_5W alone because:

- If oxytocin is added to i.v solution, water intoxication may occur causing convulsions due to antidiuretic action of oxytocin.
- If rapid infusion occurs, maternal hyperglycemia and neonatal hypoglycemia may occur.

Therefore, 5% dextrose in 0.45% saline is used instead of D_5W alone.

4- Improvement of Cerebral Edema: by osmotic diuretics.

5- Treatment of Convulsions (i.e., Eclamptic Fits):

Prophylactic treatment: Mg sulfate or diazepam should be continued throughout labor and until 24 hours postpartum.

Definitive treatment:

- Adequate airway and oxygenation should be maintained even by intubation, succinylcholine, and cricoid pressure.
- The patient should be turned to the left side with head down.
- **I.v. thiopentone** 50-100 mg immediately to terminate fits. Further fits are treated with **Mg sulfate (the first choice)** or diazepam.
- Arterial blood gases should be done because fits usually cause metabolic acidosis which necessitates administration of Na bicarbonate.

Mg Sulfate ($MgSO_4$):

Action:

- 1- It causes presynaptic inhibition of acetylcholine (ACh) release and decreases postsynaptic sensitivity to ACh. This produces:

- Central nervous depression and an **anticonvulsant action** via action on NMDA receptors.
- **Neuromuscular junction depression** and decreased muscle membrane excitability.
- 2- It causes mild relaxant effect by direct and indirect action (Ca^{++} competing). This produces:
 - **Relaxation of the uterus** and decreased uterine hyperactivity; therefore, utero-placental blood flow increases.
 - Mild vasodilatation and **antihypertensive actions**, so utero-placental, renal, and hepatic blood flow increase.

Dose:

- **4-6 g slow i.v** injection over 20-30 min then continuous infusion at **1-2 g/hour** (infusion was replaced by 5 g i.m. in each buttock).
- Additional 2-4 g can be given i.v. if fits persist.
- Continue infusion for 12-24 hours postpartum or 24 hours more after the last postpartum fit in eclampsia.

Normal Plasma Level: is 1.5-2 mEq/L.

Therapeutic Level: 4-7 mEq/L (i.e., 2-3.5 mmol/L or 4.8-8.4 mg %).

Judgment of the Therapeutic Level:

- Deep tendon reflex (knee jerk) should be present, but hypoactive. Its absence indicates impending toxicity which occurs at 10 mEq/L.
- Respiratory rate should be > 10 -12/min. If it is less, decrease or stop MgSO_4 .
- Urine output should be > 30 mL/hour. If it is less, decrease or stop MgSO_4 .

Precautions:

- 1- It **potentiates** both depolarizing and non-depolarizing **muscle relaxants**; therefore,
 - Nerve stimulator is essential.
 - Smaller doses of muscle relaxants are used.

No need for defasciculation of succinylcholine as MgSO_4 attenuates fasciculation.

Preeclampsia decreases plasma cholinesterase which potentiates suxamethonium (independent of MgSO_4 effect).

- 2- It **potentiates** both **narcotics and sedatives**; therefore, smaller doses of them should be used.

- 3- It is excreted by the **kidney**; therefore, it is used cautiously in patients with **renal diseases**.

MgSO_4 Toxicity:

Clinical picture: depends on the level of MgSO_4 .

At 5-10 mEq/L: prolonged QT interval and wide QRS complex (ECG) occur.

At 10 mEq/L: deep **tendon** reflex is lost and skeletal muscle paralysis occurs.

At 15 mEq/L: SA node and AV node block (CVS) with **respiratory** paralysis occur.

At 25 mEq/L: cardiac **arrest** occurs.

Prophylactic measure:

- Continuous clinical judgment of the therapeutic level (as above).
- Repeated measurement of serum magnesium every 2 hours.

Treatment:

- Stop MgSO_4 immediately.
- Cardiac and respiratory resuscitation should be started immediately.
- Ca^{++} is the antidote, but it is given only in severe toxicity (not used routinely) because it antagonizes the anticonvulsant effect of MgSO_4 .

Effect of MgSO_4 on the Fetus:

MgSO_4 crosses the placenta and leads to the following effects:

- Cardiovascular inhibition with **transient loss of beat to beat variability** (before delivery).
- Central nervous inhibition with **drowsiness and hypoventilation** (after delivery).
- Neuromuscular junction inhibition with **hypotonia** (after delivery).

These effects can be partially antagonized by Ca^{++} : Ca chloride 10% 20 mg/kg i.v.

Ca gluconate 10% 60 mg/kg i.v.

Anesthetic Management

Preoperative Management:

Preoperative assessment is essential by history, examination and investigations to detect the above complications.

Intraoperative Management:

Monitoring: Standard monitors are applied, in addition to:

- **Monitoring of the therapeutic level of Mg^{++} .**
- Monitoring of the circulatory volume state in severe cases by central venous pressure and pulmonary capillary wedge pressure.
- Invasive intra-arterial line for invasive blood pressure in severe cases, and blood samples for arterial blood gases.
- **Obstetric monitoring by:**
 - **tocodynamometry to monitor uterine contractions.**
 - **Cardio-scope to monitor fetal heart sound.**
 - **Fetal scalp pH to assess fetal status.**

Choice of Anesthesia:

1- Continuous Epidural Block:

It is the method of **choice** for pain relief during vaginal delivery or cesarean section provided that there is:

No circulatory volume depletion with proper control of hypotension.

No coagulopathies. Many anesthesiologists place an epidural catheter at a platelet count 80 000/ μ L.

This decision should be individualized according to the bleeding history of each patient.

Advantages:

- 1- It **decreases the level of catecholamines** (which are secreted secondary to anxiety and pain) and abolishes vasoconstriction; therefore, it allows better perfusion of utero-placental and renal vessels.
- 2- It **avoids the increase in arterial blood pressure and intracranial tension** with intubation and bearing down.
- 3- It has a **slow onset of sympathetic block and hypotension** (than in spinal block).
- 4- It **avoids** using systemic **opioids** during general anesthesia which depress respiration.

Precautions:

- 1- **Pre-hydration** before performing the block.
- 2- **Coagulation study** before performing the block.
- 3- **Early** insertion of epidural catheter because labor tends to be rapid.
- 4- **Avoid epinephrine containing local anesthetics** due to increased sensitivity of maternal vessels to catecholamines.
- 5- **Monitoring of fetal heart rate** to detect early fetal distress.

2- General Anesthesia:

Indications: • Urgent cesarean section with a distressed fetus.

- Epidural contraindications e.g., DIC.

Technique: as before in cesarean section except for:

- Patient preparation includes **treatment of preeclampsia or eclampsia**.
- **Rapid smooth crash induction with smaller sized tubes** (due to airway edema), is performed by:
 - Thiopentone (ketamine is contraindicated).
 - Suxamethonium (no need for de-fasciculation as $MgSO_4$ attenuates fasciculation).
 - **Avoid the pressor response** to intubation by:
 - Lidocaine 100 mg i.v 3-5 minutes before induction.
 - Hydralazine, labetalol, nitroglycerine, trimethaphan or nitroprusside with invasive blood pressure monitoring.
- Maintenance is done with:
 - N_2O : O_2 .
 - Volatile agents (2/3 of MAC). **Avoid nephrotoxic drugs e.g., methoxyflurane.**
 - Muscle relaxants: careful titration of the dose by using a **nerve stimulator** is essential due to the relaxant effect of $MgSO_4$. **Pancuronium should be avoided due to its sympatholytic action.**
- **$MgSO_4$ should be continued** intra- and postoperatively.
- **Ergometrine should be avoided**, except in very severe uterine atony, because it increases arterial blood pressure and eclampsia.

Postoperative Management:

Intensive care admission is essential in severe cases.

- **$MgSO_4$ should be continued** up to 24 hours in preeclampsia and 24 hours after the last postpartum fit in eclampsia.
- Anti-hypertensive drugs and i.v. fluids should be continued.
- Pain control is essential.

II) Maternal Hemorrhage during Labor

A- Antepartum Hemorrhage:

Causes:

- 1- **Placenta previa (the most common cause):** is abnormal implantation of the placenta where it encroaches upon the internal cervical os. It causes **painless vaginal bleeding** in the 2nd and 3rd trimesters. The mother is usually **hemodynamically unstable**.
- 2- **Vasa previa:** indicates presence of intra-membranous fetal vessels that overlie the cervical os in front of the fetal presenting part. It causes **painless vaginal bleeding** with decreased fetal movement and high fetal mortality. As the bleeding is from a fetal source, the mother is usually **hemodynamically stable**.
- 3- **Placental abruption:** is premature separation of the placenta from the deciduas basalis. It causes **painful vaginal bleeding**, concealed hemorrhage, and DIC.
- 4- **Uterine rupture:** causes **severe abdominal pain referred to the shoulder** due to sub-diaphragmatic irritation by intra-abdominal blood, **shock**, and disappearance of fetal heart rate.

Diagnosis:

Any antepartum vaginal bleeding is considered placenta previa until proved otherwise.

- **Abdominal ultrasound or color flow Doppler scan** is performed to:
 - confirm the presence of placenta previa by localizing the position of the placenta.
 - exclude vasa previa, placental abruption, and uterine rupture.
- **Radioisotope scan or magnetic resonance imaging (MRI)** can be used to confirm the diagnosis.
- **Double setup examination of the patient:** is rarely done nowadays and replaced by the ultrasonography. The parturient is placed in lithotomy position for vaginal examination in the operative room with everything prepared for immediate cesarean section as her abdomen is prepared and draped. Anti-hemorrhage measures are prepared and ready.
- If vasa previa is suspected, the blood present is of fetal origin. It is tested by:
 - A Wright's stain; which looks for fetal nucleated red blood cells.
 - An Apt test; as an alkaline solution is added to the blood. Adult red blood cells will rupture in this environment and turn the solution brown as opposed to fetal red blood cells, which will remain bright red.

Management:

The severity of hemorrhage is estimated by patient's vital signs, hematocrit, central venous pressure, and external blood loss, but the latter may not be related to the degree of shock.

Before vaginal examination:

- Blood volume should be restored before examination. In emergency situations, O-negative packed blood is given till the blood typing is completed.
- Two large patent venous lines should be secured.
- Two units of blood should be available in the operative room.

If urgent cesarean section or exploration for uterine rupture is indicated:

- **General anesthesia is the method of choice** with good preoxygenation and ketamine induction.
- Regional anesthesia is avoided because:
 - There is no enough time as it is an emergency condition.
 - There is a possibility of DIC.
 - Hypotension is more common.

B- Intrapartum Hemorrhage:

Uterine rupture is the most common cause. As the uterine artery blood flow is between 500-700 mL/min, the hemorrhage is usually severe and the mother suffers from shock.

Risk Factors:

- Previous uterine surgery: It is more with a vertical uterine incision than a low transverse segment incision.
- Breech extraction.
- Obstructed labor.
- Abnormal fetal position.
- Multi-parity.
- Excessive ecbolics.

C- Postpartum Hemorrhage:

It is defined as hemorrhage after delivery which exceeds 500 mL. It usually occurs after the delivery by a short time, but it can occur within 6 weeks after delivery.

Causes:

- 1- **Uterine atony:** It usually occurs with prolonged 1st stage of labor, preeclampsia, multiple parity or births, large fetus, polyhydramnios, retained placenta, or the use of tocolytics especially magnesium sulfate.
- 2- **Obstetric lacerations.**
- 3- **Uterine inversion.**
- 4- **Clotting factor defects.**
- 5- **Retained placenta and incomplete emptying of uterus.**
- 6- **Uterine rupture.**
- 7- **Placenta accreta:** The placenta is abnormal adherent to the myometrium.
Placenta increta: The placenta invades the myometrium.
Placenta percreta: The placenta invades the myometrium and the uterine serosa, with possible invasion of other structures such as bowel or bladder (figure 10-6).

Diagnosis: is confirmed by abdominal ultrasound or color flow Doppler scan.

Management:

- 1- **Resuscitation** of shocked patients.
- 2- **Recombinant activated factor VII (rF VIIa):** is used in severe hemorrhage with DIC. See before in the chapter "Pharmacological adjuncts to anesthesia and intensive care".
- 3- **Treatment of the cause:**
 - **Treatment of atony** is performed by:
 - Physical compression of the uterus by bimanual compression or uterine massage.
 - Ecbolics such as oxytocin, methergine, or prostaglandin analogues (see above).
 - **Examination under general anesthesia may be needed to repair perineal laceration.**
 - **Angiographic embolization** is done when the bleeding continues from an identifiable localized area. Embolization occurs through a radio-graphically placed catheter.
 - **Internal iliac artery ligation.**
 - **Emergency cesarean hysterectomy** is very rare.

N.B.: **Sheehan's Syndrome**

It is a **pituitary infarction** that may occur in patients with **peripartum hemorrhage**. It causes:

- Hypotension that is unrelieved by fluid resuscitation or vasopressors.
- Failure to lactate, fatigue, or cold intolerance.

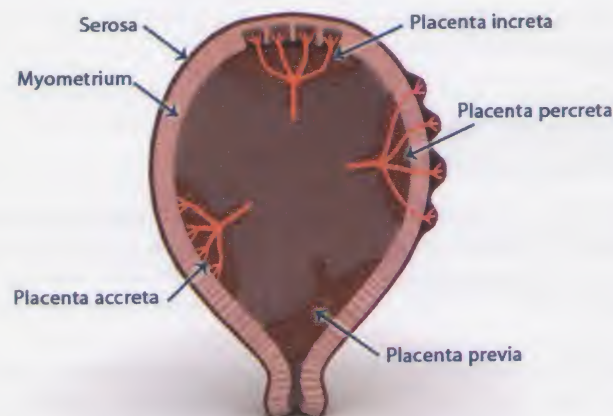


Figure 10-6: Placenta accreta and placenta previa

III) Premature or Preterm Labor

It is delivery between **20-37 weeks** of gestation.

Treatment of Premature Labor and Anesthetic Management:

- 1- **Bed rest.**
- 2- **Tocolytics:** are used to decrease uterine activity and inhibit preterm labor, for example, MgSO_4 , Ca^{++} channel blockers, indomethacin, prostaglandins inhibitors, and β_2 agonists such as **ritodrine** (*Yutopar*), yohimbine, and terbutaline.

Side Effects of β_2 Agonists:

- **Tachycardia and arrhythmias** (by β_1 action): atropine and pancuronium should be avoided. Halothane can be used with care.
- **Hypokalemia**: increases muscle relaxant sensitivity and causes heart arrhythmias.
- **Hypertension**: Ketamine is contraindicated.
- **Pulmonary edema**: Pre-hydration should be done with care.
- **Hyperglycemia**: Caution is taken in diabetic patients.
- **Fetal tachycardia and hypoglycemia**: Careful resuscitation should be done.

Therefore, **anesthesia should be delayed for at least 3 hours after stopping tocolytics** to allow β_2 actions to be dissipated.

3- If labor is still in progress, either vaginal delivery or cesarean section is planned.

Epidural or low spinal block is the method of choice and preferred to general anesthesia because:

- It provides maximum analgesia e.g., for generous episiotomy or outlet forceps.
- It provides maximum pelvic floor relaxation.
- It avoids exposure of a relatively more sensitive premature fetus to neurological depressant anesthetic drugs or their systemic toxicity.

4- **A premature neonate** is:

- more susceptible to **asphyxia** as there is increased risk of umbilical cord compression.
- more susceptible to **intracranial hemorrhage** during vaginal delivery due to soft cranium.
- more susceptible to **idiopathic respiratory distress syndrome** due to inadequate surfactant which reaches an adequate level after 35 weeks of gestation.

Therefore, complete fetal resuscitation should be prepared before delivery.

IV) Multiple Gestation

Anesthetic Problems:

- a- **Maternal**: - All physiological changes of pregnancy are more exaggerated e.g., more aorto-caval compression due to the larger sized uterus than singleton pregnancy.
- Pregnancy induced hypertension.
 - Maternal hemorrhage.
- b- **Fetal**: - Prematurity.
- Breech presentation.
 - The 2nd baby is more prone to depression and asphyxia due to partial separation of the placenta.

Technique:

- Epidural block is preferred.
- During the interval between the 1st and the other babies, do not give ecbolics or opioids.

V) Maternal Heart Diseases

Anesthetic Problems:

- 1- In western countries, the most common causes of heart diseases during pregnancy are:
- Congenital heart diseases (70-80%) due to the advances in surgical and medical therapy, allowing these women to survive into childbearing age.
 - Ischemic heart diseases.
 - Dilated peripartum cardiomyopathy.

In Egypt, the most common cause of heart diseases during pregnancy is rheumatic heart diseases.

2- During pregnancy and labor, **physiological changes** can affect heart disease e.g., increased cardiac output **precipitates congestive heart disease** in 50% of patients who have dyspnea with minimal activity.

3- Some **cardiovascular drugs can cross placenta and affect the fetus** such as:

- Lidocaine causes fetal depression.
- Propranolol causes fetal bradycardia.
- Digitalis causes fetal toxicity.

4- Preoperative **antibiotic prophylaxis against endocarditis** during vaginal delivery such as:

Ampicillin 2 g i.v/i.m. + Gentamycin 1.5 mg/kg i.v/i.m. are given 1 hour before labor, and continue during labor and 2 days after labor.

During cesarean section, the risk of bacterial endocarditis is minimal unlike the vaginal delivery and episiotomy where there are commensal bacteria in the vagina; therefore, during cesarean section, antibiotic prophylaxis is usually with a broad spectrum antibiotic.

5- **Diseases** are classified into 2 groups according to their management:

Diseases	<ul style="list-style-type: none"> • Mitral regurgitation • Aortic regurgitation • Cardiomyopathy of pregnancy • Dissecting aortic aneurysm • Congenital heart disease with left to right shunt. 	<ul style="list-style-type: none"> • Mitral stenosis (90% of cases) • Aortic stenosis • Primary pulmonary hypertension • Coarctation of the aorta • Congenital heart disease with right to left shunt or bidirectional shunt
The primary aim	Avoid increased preload (i.e., venous return) and afterload (i.e., systemic vascular resistance)	Avoid decreased preload and afterload
Choice of anesthesia	Continuous lumbar epidural block is preferred because it decreases the preload and afterload; therefore, it decreases pulmonary congestion and edema.	General anesthesia is preferred Regional block is avoided and if it is necessary, opioids alone are used.

The **anesthetic management** of these diseases is **discussed** in their corresponding chapters.

Special Precautions of Cardiac Diseases during Pregnancy:

1- **Congenital Heart Diseases:** in addition to the usual management, other precautions include:

- Care is taken for removal of small air bubbles such as during performing **loss of resistance** techniques during **epidural anesthesia**, **saline** should be used instead of air especially in patients with left to right shunt e.g., ventricular septal defects.
- Patients with right to left shunt e.g., **Fallot tetralogy** should receive **adequate analgesia** during labor to prevent excessive sympathetic stimulation which increases the shunt.
- Patients with **coarctation of the aorta** have hypotension in the lower half of the body including the utero-placental blood flow; therefore, maintaining the blood pressure and blood volume is essential for placental circulation and fetal viability. It should be assessed by invasive blood pressure where the **systolic blood pressure** should be kept **above 100 mm Hg** to ensure maintaining the uterine blood flow. The **post-ductal left radial artery** is preferred than the pre-ductal right radial artery, because the former represents the blood pressure in the lower half of the body.

2- **Ischemic Heart Diseases:** in addition to the usual management, other precautions include:

Myocardial ischemia during pregnancy is usually due to coronary vasospasm rather than coronary artery diseases.

- Symptoms of ischemic heart **mimic the symptoms** of normal pregnancy such as dyspnea, leg edema, and poor exercise tolerance.
- Electrocardiographic (ECG) **changes mimic** that occur in normal pregnancy such as sinus tachycardia, left axis deviation, ST segment depression, flattened or inverted T waves, and Q wave in lead III, making diagnosis of myocardial ischemia by ECG difficult. Therefore, **careful differentiation** is required and **echocardiography is essential for this differentiation**.
- **Adequate analgesia** during labor or cesarean section e.g., by a dense epidural block is **essential**. **Epinephrine is avoided** in the epidural test dose.
- **Phenylephrine** is the vasopressor of choice for maternal hypotension. **Ephedrine** should be **avoided** due to the tachycardia it produces that is undesirable in patients with ischemic heart diseases.
- Patients on the **new antiplatelet drugs** e.g., clopidogrel should **not receive neuraxial anesthesia**.

3- **Peripartum Cardiomyopathy:** in addition to the usual management, other precautions include:

It is dilated idiopathic cardiomyopathy that occurs usually in the last month of pregnancy and lasts until 5 months postpartum.

- As above, **many of the cardiovascular symptoms mimic** those of normal pregnancy (as above), in addition to the heart murmurs and radiographic cardiomegaly that can occur during normal pregnancy. N.B.: **Hepatomegaly and congested neck veins** do not occur during pregnancy, but **only occur with dilated cardiomyopathy** and heart failure.
- **Angiotensin-converting enzyme inhibitors (ACE inhibitors);** although **contraindicated during pregnancy** due to **teratogenicity**; can be **used as a postpartum treatment**.

VI) Diabetes Mellitus with Pregnancy

Anesthetic Problems:

1- Maternal:

There is increased incidence of: • Pregnancy induced hypertension.

- Diabetic ketoacidosis especially in the 2nd and 3rd trimester.
- Polyhydramnios.

Insulin is used because it does not cross the placenta (unlike oral hypoglycemics which cross the placenta and cause neonatal hypoglycemia).

2- Fetal:

There is increased incidence of: • Large baby size.

- Respiratory distress syndrome.
- Premature labor.
- Congenital diseases and anomalies.
- Fetal hypoglycemia.
- Intra-uterine fetal death.
- Shoulder dystocia.

VII) Amniotic Fluid Embolism

Incidence: is between 1: 8000 and 1: 80 000 pregnancies.

Pathology:

The amniotic fluid, containing fetal squamous cells, reaches the maternal circulation and causes pulmonary vascular occlusion due to:

- **Mechanical obstruction.**
- **Humoral obstruction** by prostaglandin release, histamine, serotonin, and leukotrienes which produce pulmonary vasoconstriction.

The site of communication between the amniotic fluid and maternal circulation can occur at:

- the level of the endocervical vessels,
- the level of the placenta, and
- at a uterine trauma site.

Clinical Picture:

It is usually **sudden and unpredictable** and occurs during labor or immediately post-partum.

1- It is similar to any **acute pulmonary embolism** such as:

- **Respiratory distress**, dyspnea, and hypoxia which in turn causes **fits in 10%** of cases.
- Tachycardia, hypotension, up to **circulatory collapse**.

If the primary resuscitation is successful,

- **Pulmonary edema** (**cardiogenic** with left ventricular failure or **non-cardiogenic** with acute respiratory distress syndrome) may occur.
- **DIC** may follow.

Mortality rate is 80-86%.

2- Severe vaginal bleeding may occur due to DIC and uterine atony.

Investigations:

1- ECG shows signs of **right ventricular strain** as right axis deviation, inverted T wave in leads V₁-V₄, and right bundle branch block.

2- **Chest x-ray** shows **pulmonary oligemia** (due to pulmonary vascular occlusion), and **atelectasis**.

3- **Arterial blood gases** show **decreased PaO₂** due to increased alveolar dead space and **decreased PaCO₂** due to hyperventilation.

4- **Diagnosis is confirmed by finding fetal debris** in: • The central venous blood of the mother.
• Sputum.
• Lung tissue (at autopsy).

Differential Diagnosis:

- 1- Other causes of pulmonary embolism.
- 2- Pulmonary aspiration of gastric contents.
- 3- Eclampsia or local anesthetic drug toxicity (in presence of convulsions).

Treatment:

It is nonspecific and supportive.

- **Respiratory support** as 100% oxygenation and mechanical ventilation.
- **Circulatory support** as inotropes, vasopressors, replacement of blood and clotting factors (for DIC).
- **Hysterectomy** is indicated to treat severe uterine atony.

VIII) Ectopic Pregnancy

Anesthetic Problems:

- 1- Patients may be **normovolemic** with mild abdominal pain up to **severe shock** with major internal hemorrhage.
- 2- **Severe hemorrhage** may occur **intraoperatively**; therefore,
 - Cross matched **blood** should be available in the operating theater.
 - At least one large bore **i.v. cannula** should be inserted before induction.
 - **Rapid sequence crash induction**, after a period of preoxygenation, with ketamine or etomidate if hypovolemia is anticipated with the surgeon standing by.
 - Regular coagulation screens should be done as DIC may occur with severe hemorrhage.
- 3- **Laparoscopic surgery for ectopic pregnancy** can be performed especially when the patient is hemodynamically stable. With severe hemorrhage, **pneumo-peritoneum may impede venous return to the heart** with sudden fall in blood pressure. If this occurs, the surgeon should be advised to proceed immediately to laparotomy.

IX) Acute Fatty Liver of Pregnancy

Incidence: is between 1: 7000 and 1: 16 000 pregnancies.

Cause: is unknown. In some cases, the mother or the fetus has a genetic defect of fatty acid beta oxidation and there is micro-vesicular fatty infiltration of hepatocytes.

Clinical Picture:

It occurs in the last trimester of pregnancy or immediately postpartum.

- Prodroma of nausea, vomiting, anorexia, and malaise for 1-2 weeks.
- Epigastric pain or right upper quadrant pain.
- Variable degree of jaundice occurs after the prodroma.
- Hypertension with or without proteinuria and edema. Some authors consider the disorder to be a variant of preeclampsia as many of these patients have pregnancy-induced hypertension and HELLP syndrome.
- Transient diabetes insipidus.
- In severe cases, ascites, hepatic encephalopathy, hypoglycemia, DIC, metabolic acidosis, renal failure, pancreatitis, and gastrointestinal bleeding may occur.
- Fetal mortality is high.

Investigations:

- 1- Complete blood picture shows leukocytosis $> 20\,000/\mu\text{L}$ and anemia.
- 2- Liver affection shows increased AST, ALT, bilirubin, and alkaline phosphatase, and decreased serum albumin, and serum glucose.
- 3- If DIC occurs, fragmented red blood cells, micro-angiopathic hemolysis, prolonged prothrombin time and partial thromboplastin time, decreased fibrinogen and platelets, and increased fibrin degradation products are present.
- 4- Renal function tests shows elevated serum urea, blood urea nitrogen, and serum creatinine.
- 5- If pancreatitis is present, serum lipase and amylase are elevated.
- 6- Liver biopsy shows microvascular fat within the hepatocytes by frozen tissue section or electron microscopy. Care is taken if there is coagulopathy.

Treatment:

- 1- **Patient support** and stabilization similar to that with preeclampsia such as airway control, magnesium sulfate or hydralazine for hypertension, i.v. fluids, and desmopressin for diabetes insipidus.
- 2- **Delivery** is performed as soon as possible, either by vaginal or cesarean section, **by general anesthesia** due to presence of coagulopathy.
- 3- Liver support by:
 - i.v. glucose and early oral nutrition,
 - oral lactulose 20-30 g (30-45 mL)/1-2 hours to induce diarrhea and soft stools, for 2-4 times/day to decrease production of ammonia.
 - oral neomycin 0.5-1 g/6 hours.
- 4- Liver transplantation for very severe cases.

Other Minor Obstetric Procedures

1- Dilatation and Curettage (D & C)

Anesthetic Problems:

1- **Lithotomy positions:** see later chapter of "Anesthesia and genitor-urinary surgery".

2- **Cervical dilatation:**

- Intraoperatively: It causes **vagal stimulation** leading to reflex laryngospasm and bradycardia; therefore, deep anesthesia is required.

- **Postoperatively:** Patients have **severe pain**; therefore, analgesia is important by ketorolac or diclofenac.

3- **Uterine stimulants (ecbolics):** such as oxytocin, methergine, and prostaglandins. They are discussed above.

4- **Emergence from anesthesia:** may be accompanied by profound **emotional upset** due to loss of the baby. Recovery staff should be prepared to deal with the patient sympathetically.

2- Endoscopic Endometrial Resection:

Anesthetic Problems:

1- Lithotomy position with its precautions and complications.

2- Unexpected great blood loss may occur. It is difficult to be estimated, as it is usually diluted with irrigation fluid.

3- Absorption of irrigation fluid may cause:

- Hyponatremia.
- Hypervolemia which decreases plasma osmolality and may produce pulmonary edema.
- Hypothermia.

The clinical picture is **similar to** transurethral resection of the prostate syndrome (**TURP syndrome**), but it occurs **in a female patient**.

Postpartum Tubal Ligation

It is the most common type of surgery performed during the early postpartum period.

Anesthetic Problems:

All the **physiological changes of pregnancy** return to the pre-pregnant state within **6 weeks postpartum**, but in different degrees.

1- The **MAC** returns to the normal by the **3rd day** post-delivery.

2- The **doses of local anesthetics** in regional anesthesia return to normal within **24-36 hours** after delivery.

3- **Functional residual capacity** returns to normal within **48 hours** post-delivery.

4- At 48 hours postpartum, the **cardiac output** is slightly lower than pre-labor values.

2 weeks postpartum, it decreases to 10% higher than the pre-pregnancy value and slowly returns to pre-pregnancy value within **12-24 weeks** postpartum.

5- The **plasma volume** returns to normal by **6 days** post-delivery, but it increases sharply up to 1 liter 24 hours after delivery due to diversion of blood from the placenta to the main circulation (auto-transfusion), although there is blood loss during labor (about 500 mL).

6- The **risk of aspiration** is still present; therefore, all precautions should still be taken.

- Gastric **emptying**, gastric **volume**, and **pH** return to **normal** within **1-3 days**, but the incidence of **nausea and vomiting** is less due to:
 - relieved mechanical distortion of the stomach.

- relieved labor pain.

- rapid decline of the progesterone level.

Laparoscopic Sterilization

Sterilization and tubal ligation may be performed by laparoscopy. It is relatively a simple procedures. Many methods of local anesthesia have been used:

- Instillation of local anesthetic through the uterus to the inside of the Fallopian tubes.
- Injection of local anesthetic into the mesosalpinx.
- Instillation of local anesthetic into the pouch of Douglas via an epidural catheter inserted through the abdominal wall.

None of these methods is totally effective and some patients may still require an opioids.

Anesthesia for Non-Obstetric Surgery in Pregnant Patients

All elective surgeries should be postponed **till 6 weeks after delivery** and **only emergency surgery should be performed during pregnancy** especially in the 1st trimester. The most common surgeries during pregnancy are excision of an ovarian cyst, appendicectomy, cervical circlage, trauma, and breast mass biopsy. In the same time, anesthesia might be applied in early undiagnosed pregnancy.

Anesthetic Problems:

1- Physiological Changes of Pregnancy:

They are discussed in more details in the beginning of this chapter. They can affect the anesthetic management especially:

- Decreased local and inhaled anesthetic doses.
- Decreased functional residual capacity.
- Increased gastric acidity, so there is an increased risk of regurgitation.
- Aorto-caval compression.

2- Teratogenicity of Anesthetic Drugs:

- Three periods of pregnancy can be affected:

a- **The 1st 15 days** post-conception:

Effects of drugs are either **lethal or with no effects**.

b- From **15-56 days** post-conception:

It is the **period of organogenesis**; drug exposure may cause major developmental abnormalities.

c- **After 56 days** post-conception:

It is the **period of organ growth**; drug exposure may cause either growth retardation or minor morphological abnormalities.

- **Drugs used during pregnancy and their FDA categories** are discussed in chapter 4 "Pharmacological adjuvants to anesthesia and intensive care".

- Most drugs have not been studied in pregnancy during the Food and Drug Administration (FDA) approval period, so most new drugs will be placed in category C. For this reason, many drugs used routinely during pregnancy are older ones, with an established record of safe use i.e., **time-tested drugs or anesthetics** e.g., halothane and morphine are used instead of new agents e.g., desflurane, remifentanyl.

- Generally, no documents are reported in human as regard teratogenicity of any anesthetic agents except:

- **N₂O** carries much controversy because it produces:
 - inhibition of methionine synthetase which affects **myelin** synthesis.
 - inhibition of thymidylate synthetase which affects **DNA** synthesis.
 - an increase in the sympathetic activity which decreases utero-placental flow. This is prevented by addition of volatile agents.
 - teratogenic effects in animals on prolonged exposure (not in humans).

Therefore, there must be **caution** on its use in pregnancy especially in the first trimester.

• **Benzodiazepines**, when used in the first trimester, are associated with **cleft lip** anomalies, but other studies fail to detect this effect.

• In USA and UK, large retrospective studies suggest that female anesthesiologists and the wives of male anesthesiologists had an increased incidence of spontaneous abortion and congenital anomalies in babies than non-operating room physicians. It is suggested that chronic exposure to trace anesthetic gases is the cause.

3- Risk of Premature Labor Initiation:

There is no evidence that a specific anesthetic agent or technique is associated with a higher or lower incidence of premature delivery; actually the underlying pathology necessitating the operative intervention is the affecting factor e.g., premature labor in patients undergoing a cervical circlage.

4- Adequacy of Utero-Placental Perfusion:

They are discussed in more details in this chapter. Hypotension, stress responses, extreme hypocapnia (by hyperventilation) should be avoided.

Anesthetic Management:

Preoperative Assessment: It should be done as usual in addition to:

- **Pregnancy test** that should be in mind in all females in the child-bearing period.
- **Obstetric consultation** that should be obtained before surgery to document the preoperative well being of the fetus.

- Premedications:

- 1- Drugs to **prevent aspiration** such as antacids are given as usual.
- 2- **Glycopyrrolate** is used as an anticholinergic and an antisialagogue because it does not cross the placenta.
- 3- **Sedatives** are given to decrease the stress of the patients which decreases the maternal catecholamines and enhances the utero-placental blood flow.
- 4- **Tocolytics** are used if regular uterine activity occurs.

Intraoperative Management

Monitoring: The standard monitors are applied in addition to the following:

- **Fetal heart rate** is needed in some cases. It is assessed by Doppler after 20-24 weeks of gestation to detect decelerations and fetal bradycardia which indicate inadequate utero-placental circulation. Loss of beat to beat variability is not indicative after anesthesia or sedation as it normally occurs with them.
 - **Uterine activity** is assessed by **computerized toco-dynamo-gram (CTG)** to detect premature labor as regular uterine activity necessitates early treatment with tocolytics.
- Both monitors should be done pre-, intra-, and postoperatively along all the recovery period.

Choice of Anesthesia:

A-Regional anesthesia:

- It is **preferred** to general anesthesia although there is no evidence that general anesthesia has adverse effects.
- **Spinal block** is preferred to epidural block due to less doses of local anesthetics used.

B- General anesthesia:

The same precautions are taken as with cesarean section such as left lateral tilt, preoxygenation, rapid sequence induction, cricoid pressure,...etc, in addition to:

- **N₂O is controversial.** Omit it or use a small concentration.
- Use **time-tested agents** e.g., halothane, morphine.
- **Avoid ketamine** > 2 mg/kg as it causes uterine hypertonicity.
- **Slow reversal** of muscle relaxants to prevent acute increase in acetylcholine which may induce uterine contractions.

Special Conditions in Pregnant Patients:

1- Appendicitis:

- The incidence of gangrenous appendix is increased during pregnancy because the enlarged uterus pushes the appendix away from the abdominal wall causing little pain. Therefore, delayed diagnosis occurs.
- There is an increased incidence of pulmonary edema and acute respiratory distress syndrome (ARDS) if tocolytics are used especially if one of the following risk factors is present:
 - Gestational age is > 20 week.
 - Preoperative respiratory rate is > 24/min.
 - Preoperative temperature is > 100.4 F. degree.
 - Fluid load is > 4 liters in the 1st 24 hours.

2- Deliberate Hypotensive Anesthesia:

It is performed **only if necessary**; nitroglycerine, hydralazine and nitroprusside are good choices, but prolonged infusion of nitroprusside should be avoided because it may cause fetal cyanide toxicity due to the immature liver.

3- Cardiac Surgery and Cardiopulmonary Bypass:

It is performed **only if emergency**, but with the following precautions:

- If possible, surgery should be **delayed until second trimester** when the major risk of teratogenicity e.g., from cardiac medications, x-rays, and low flow or hypoxic states has passed and preterm labor is less likely.
- **Continuous fetal echocardiography monitoring is essential.** It can be used to optimize the mean arterial pressure and the flow rate during bypass. Fetal bradycardia occurs at the onset of cardiopulmonary bypass and slowly returns to the normal rate. **Higher flow rates and mean pressure** of cardiopulmonary bypass **may be beneficial** during pregnancy to maintain uterine blood flow and fetal oxygenation.
- Hypothermia is used successfully, but **some advocate warm bypasses.**
- **Circulatory arrest** during bypass is **not recommended.**

Nowadays, it has been found that maternal mortality is the same as the non-pregnant state; therefore, do not withhold cardiac surgery if indicated.

4- Laparoscopic Surgery e.g., cholecystectomy.

- Although pregnancy has been considered a contraindication to laparoscopic procedures in the past, an increasing number of such procedures are being performed in the parturient successfully.

- During pneumo-peritoneum of a pregnant female, there is a combination of the physiological and anatomical changes of pregnancy such as increased blood volume, cardiac output, the supine hypotension syndrome, decreased lung volumes and increased risk of aspiration, in addition to the physiological changes of pneumo-peritoneum, hypercarbia, and positional changes.

These effects may increase hypercarbia, hypoxia, acidosis, and decrease utero-placental perfusion. These effects should be monitored and managed during the procedure by the anesthesiologists.

- Generally, laparoscopic procedures **are safe in parturients** and the following precautions should be taken:
 - Maternal **end-tidal CO₂** should be maintained at normal values.

- An **open technique for trocar placement** should be chosen.

- An arterial line is inserted to assess **maternal blood gases** with long operations.

- **Intra-abdominal pressure** should be kept as **low** as possible.

- Operative and insufflation **time** should be decreased to the minimum.

- **N₂O** should be used **instead of CO₂** as an insufflating gas because CO₂ pneumoperitonium may produce **fetal respiratory acidosis** (although it does not cause any fetal hemodynamic changes).

- **Fetal shielding** during cholangiograms should be used.

5- Trauma:

- **Early ultrasound** should be done in emergency room to determine **fetal viability**.

- **Shielding** of the fetus whenever possible (< 5 rad exposure has no risk to the fetus), if x-ray is used. MRI and ultrasound are safer.

- **Indications of emergency cesarean section** after trauma:

- Stable mother with distressed fetus.

- Traumatic uterine rupture.

- A gravid uterus interfering with intra-abdominal repair in the mother.

- A mother who will die, but with a viable fetus.

6- Neurosurgery: as aneurysmal or A-V malformation repair.

It can be done with the following precautions:

- **Induced hypotension** is performed only if necessary with fetal monitoring.

- **Avoid hyperventilation** because it shifts O₂-Hb curve to the left which decreases maternal CO₂ and O₂ release.

- Very **high dose mannitol** may cause **fetal dehydration**.

- **Fetal shielding** is needed.

- **Endovascular treatment** of acutely ruptured intracranial aneurysms has been done successfully during pregnancy, thus avoiding craniotomy.

7- Fetal Surgery:

It is only done in a few centers for limited indications. It has the following problems:

- Postoperative preterm labor can be initiated.

- Maternal morbidity can occur due to pulmonary edema.

- Preoperative indomethacin and perioperative MgSO₄ are used as tocolytics.

- High doses of inhalational agents are used for maternal and fetal anesthesia and for uterine relaxation during surgery.

More details are discussed in the chapter of "Anesthesia and fetal surgery".

Postoperative Management

- 1- Continue monitoring the fetal heart rate and uterine activity.

- 2- Postoperative pain relief should be done by:

- Systemic medications (they may decrease fetal heart rate variability).

- Regional techniques.

- 3- Care is taken to avoid deep venous thrombosis.

- 4- Maintain maternal oxygenation and left uterine displacement especially in the late trimester.

Anesthesia for Assisted Reproductive Technologies (ART)

Assisted reproductive technologies include:

- **Hormonal stimulation:** by a gonadotropin releasing hormone agonist, leuprolide acetate (*Lupron*) and human menopausal gonadotropin. Over stimulation may lead to **ovarian hyper-stimulation syndrome**.
- **Oocyte retrieval:** by a trans-vaginal ultrasound (commonly used) or laparoscopy (rarely used), while the patient is in the **lithotomy position**. This step may be **complicated by** hemo-peritonium, iliac hematomas, infection and abscess formation. It usually requires **anesthesia**.
- **In vitro fertilization:** of an oocyte with spermatozoa in a culture medium.
- **Embryo transfer:** to the fallopian or uterine cavities. Usually it does not require anesthesia.

Effect of Anesthesia of ART:

- 1- **Local anesthetics** appear to have **minimal impact** on ART outcome.
 - 2- **General anesthesia** produces lower cleavage rates of oocytes when compared with epidural anesthesia.
 - **Thiopental, midazolam, fentanyl, and propofol** produce **no effects** on ART outcome.
 - Although N_2O inhibits methionine synthetase enzyme, it has **no effect** on ART outcome.
 - **Halothane** increases the number of abnormal mitosis and **decreases clinical pregnancy** and delivery rates.
 - **Isoflurane** has a **negative effect on cell cleavage**.
 - Caution is advised on using new volatile agents such as sevoflurane or desflurane.
 - 3- **Antiemetics:** such as **droperidol and metoclopramide** elevate **serum prolactin** which impairs ovarian follicle maturation and corpus luteum function and produce a **negative effect** on ART outcome.
- All these effects are still under research.

Anesthetic Management:

Preoperative Management:

- Preoperative assessment, investigations, and premedications are conducted **as usual**.
- They are treated as a **day-case anesthesia** with its precautions.

Intraoperative Management:

- **Lithotomy position** with its precautions and complications.
- **Choice of anesthesia:**

1- Paracervical block:

Disadvantages: Patients usually suffer from discomfort. This indicates that paracervical anesthesia blocks pain sensation in the vagina and not ovarian area.

2- Conscious sedation:

Disadvantages: It is associated with:

- Loss of consciousness.
- Patient movement in critical times.
- Possibility of delayed recovery.

3- Regional anesthesia: Both epidural and spinal anesthesia are used.

Spinal anesthesia may be preferable to epidural anesthesia because of lower systemic absorption and hence lower follicular levels of anesthesia, in addition to more rapid turnover.

4- General anesthesia: is performed by total i.v. anesthesia with propofol or by volatile anesthesia.

The above 4 techniques are suitable for trans-vaginal aspiration of the follicles, but only general anesthesia is suitable for laparoscopic aspiration of the follicle.

Postoperative Management:

- **Pain relief** is usually done by opioids such as fentanyl. **Non-steroidal anti-inflammatory drugs** should be **avoided** because they change the prostaglandins which affect embryo implantation.
- **Nausea and vomiting** are common complications, but **droperidol and metoclopramide** are **avoided** due to their effect on prolactin level.

Ovarian Hyper-Stimulation Syndrome

Definition:

It is an iatrogenic condition that occurs with ovarian hyper-stimulation (for in vitro fertilization) using **gonadotropin preparations** or rarely other preparations.

Pathophysiology:

Cytokines and renin-angiotensin-system are involved in the pathogenesis. It is characterized by growth of multiple follicles with **massive extra-vascular protein-rich fluid shift** which leads to:

- Hypovolemia, hemoconcentration, thromboembolic phenomena, and electrolyte disturbances.

- Tension ascites.
- Renal failure.
- Acute respiratory distress syndrome (ARDS).
- Cerebro-vascular problems.
- Liver dysfunction and gastro-intestinal problems.

It may be a fatal condition.

Intensive Care Unit (ICU) Considerations of Pregnant Patients

1- Physiological Changes of Pregnancy:

They are discussed in this chapter in details.

2- Patient Position:

The pregnant patient should be in left lateral tilt; see before.

3- Monitoring:

Monitoring of **the mother and the fetus** should be continued as long as the patient is in ICU. It is similar to that during anesthesia; see before.

4- Drugs Used during Pregnancy and Teratogenesis:

The physician should choose between a potentially teratogenic effect and life-sustaining pharmacological intervention for which there is no good alternative. For more details, see above.

5- Image Studies and Pregnancy:

a- Ionizing radiation such as x-ray and CT scan:

- It causes a **human teratogenicity** especially abdominal, lumbar spine, pelvic, hip, and femur, pyelography, barium enema study, and hystero-salpingography. In head and chest studies, there is minimal exposure to the fetus. The **uterus and fetus should be shielded** whenever possible.
- Ionizing radiation produces microcephaly, mental retardation, retarded growth, various structural abnormalities, and increased risk of childhood cancer after prenatal x-ray exposure such as leukemia. The most vulnerable period for the fetus is from 8-15 weeks of gestation.

b- Iodinated contrast media: can be **used** during pregnancy. They are considered category D in FDA classification. See chapter of "Pharmacological adjuvants to anesthesia and Intensive care".

c- Radionuclide scans: are **used cautiously** during pregnancy. Radioactive iodine is harmful to the thyroid of the fetus especially after 10 weeks of gestation.

d- Ultrasonography:

- **Diagnostic ultrasonography** is safe.
- **Therapeutic ultrasonography** produces tissue heating in animal; therefore, it is **contraindicated in pregnancy**.

e- Magnetic resonance imaging (MRI): is **discouraged during early pregnancy**, although there are no reports of adverse human fetal effects.

6- Nutrition:

Pregnant patients are **more prone to starvation, undernutrition, and starvation ketosis** than non-pregnant patients due to depletion of maternal glucose by the feto-placental unit. This increases infant mortality and decreases birth weight. Therefore, the following precautions should be considered in ICU stay:

- **Oral or nasogastric tube** nutrition should be **started early** in the ICU.
- **Peripheral nutritional supplementation** is essential if **starvation** is expected in **durations less than 7 days**.
- **Total parenteral nutrition** via a central line should be considered if **starvation** is expected **more than 7 days** e.g., patients with intractable nausea and vomiting of pregnancy when oral or enteral tube feeding are contraindicated.

7- Medico-Legal Aspects:

- A woman in the ICU who is found to be pregnant should be **given complete information** on the timing and dosages of drugs and diagnostic agents used in her care (before or after 56 days of gestation as above). It may be helpful to refer such a patient and her family to a **medical geneticist or a prenatal diagnostic center for counseling** and possible diagnostic procedure.
- It is advisable to obtain an **obstetric ultrasound examination** as early as possible during the pregnant patient's stay in the ICU. **Fetal abnormalities** apparent at that time are probably preexisting conditions

and not the result of medications given in the ICU. Furthermore, this will **document gestational age** and establish a **baseline** to assess **fetal growth**.

8- Delivery in ICU (Normal Labor or Cesarean Section):

- It can be done **in the ICU for unstable patients** without transferring to the delivery room by **experienced personnel** with analgesia/anesthesia techniques according to the patient's condition.
- A **peri-mortem cesarean section** in the ICU should be performed if the mother has died and an attempt is being made to salvage the fetus; therefore, **necessary instruments** for cesarean section should be **kept at or near the bedside**. The **early delivery** of the infant **after maternal death** is associated with **more infant survival**. Normal infant survival is associated with delivery **within 5 minutes** of maternal death. More than 5 minutes delay is associated with less infant survival; therefore, some authorities, including the American Heart Association suggest that **cesarean section should be started within 4-5 minutes of initiation of cardiopulmonary resuscitation**.
- **Brain dead pregnant patients are maintained for long periods on life support in order to allow growth and maturation of the fetus.**

9- Cardio-Pulmonary Resuscitation (CPR) in the Pregnant Women:

The American Heart Association has recommended the **standard resuscitative measures** and procedures as in non-pregnant patients without modification with the following notes:

- After 20 weeks' gestation, **left lateral tilt** of the patient is essential.
- After 20 weeks' gestation, a **peri-mortem cesarean section** should be done if routine advanced cardiac life support (ACLS) protocols are ineffective.
- **Cricoid pressure and intubation** should be done **as soon as possible** due to high risk of aspiration.
- **Adrenaline** is used as **usual** although its effect on uterine contractions may cause detrimental effects on the fetus.

10- Management of High Risk Complicated Pregnancy:

As discussed before.

Anesthesia for Gynecological Surgery

General Problems:

1- Patients with gynecological problems tend to be **young and fit**. Patients with incontinence or **cancer** surgery tend to be **old** and with medical diseases.

2- There is increased risk of **deep venous thrombosis**; therefore,

- Prophylactic low dose **heparin** should be given.
- Graduated **compression stocking** should be ready.
- Estrogen containing oral contraceptive **pills** (if taken by the patient) should be stopped **for 2-6 weeks** before surgery. This is not necessary in minor gynecological procedures as dilatation and curettage.

3- Some patients have **menorrhagia**; therefore, hemoglobin concentration is mandatory preoperatively.

4- Increased risk of postoperative **nausea and vomiting**. Therefore, prophylactic antiemetics are necessary.

5- In major procedures such as radical vulvectomy or pelvic exenteration (figure 10-7), care should be taken as regards:

- **Major blood loss**; therefore, - preoperative assessment of hemoglobin must be done.
 - good i.v. access must be established.
 - good blood loss monitoring is mandatory.

- **Hypothermia.**

- **Severe postoperative pain**; therefore,

- epidural anesthesia is preferred to general anesthesia.
- opioids can be administered e.g., by patient controlled analgesia.

6- In **hysteroscopy**, a syndrome like trans-urethral resection of prostate (**TURP syndrome**) can occur, but in female patients due to irrigation with nonionic isotonic solutions such as glucose or glycine.

7- Surgery may be managed as a **day case anesthesia** with its precautions.

8- **Vagal stimulation is common** as during cervical dilatation, traction on the pelvic organs or the mesentery, or during laparoscopic procedures.

9- **Complications of position** e.g., lithotomy position.



Figure 10-7: Multislice triphasic CT of the abdomen and pelvis of the same patient showing a large pelvi-abdominal uterine mass suggestive of underlying malignancy.

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NEONATAL & FETAL RESUSCITATION

11

- Fetal physiology
- Fetal and neonatal resuscitation
- A) Antepartum fetal evaluation and resuscitation
- B) Intrapartum fetal (neonatal) evaluation and resuscitation
- C) Postpartum neonatal evaluation and resuscitation (at birth)
 - Protocol of neonatal resuscitation
 - Artificial positive pressure ventilation of the newly born neonates

- Chest compression of the newly born neonates (cardiac resuscitation)
- Neonatal evaluation and resuscitation
- Drug therapy in neonatal cardiopulmonary resuscitation
 - Immediate neonatal emergency
 - A) Medical neonatal emergency
 - B) Surgical neonatal emergency

Fetal Physiology

A) Fetal Circulation

• The placenta, which receives nearly $\frac{1}{2}$ the cardiac output of the fetus is responsible for respiratory gas exchange. As a result, the lungs receive little blood flow and the pulmonary and systemic circulations are parallel instead of in series, as in adults.

This arrangement is made possible by 2 cardiac shunts: - the foramen ovale and

- the ductus arteriosus.

• Well-oxygenated blood from the placenta (80% SaO_2) mixes with venous blood returning from the lower body (25% SaO_2) and flows via the inferior vena cava into the right atrium. Up to $\frac{1}{2}$ of the well-oxygenated blood in the umbilical vein can pass directly to the heart via the ductus venosus, bypassing the liver. The remainder of the blood flow from the placenta mixes with blood from the portal vein (via the portal sinus) and passes through the liver before reaching the heart. The latter may be important in allowing relatively rapid hepatic degradation of drugs (or toxins) absorbed from the maternal circulation.

• Right atrial anatomy preferentially directs the main stream of blood flow from the inferior vena cava (67% SaO_2) through the foramen ovale into the left atrium. Left atrial blood is then pumped by the left ventricle to the upper body (mainly the brain and the heart) (62% SaO_2).

• Poorly oxygenated blood (30% SaO_2) from the upper body returns via the superior vena cava to the right atrium.

• Right atrium anatomy preferentially directs the flow from the superior vena cava into the right ventricle. Because of high pulmonary vascular resistance, 95% of the blood ejected from the right ventricle is shunted across the ductus arteriosus into the descending aorta, and back to the placenta (with low systemic vascular resistance) and lower body (figure 11-1).

• Pulmonary vascular resistance is high (high pressure low flow circuit) because:

- There is a large arteriolar muscle mass which causes great vasomotor response.
- Pulmonary blood flow is less sensitive to neuronal (less autonomic nerve endings) and endocrinal stimuli.

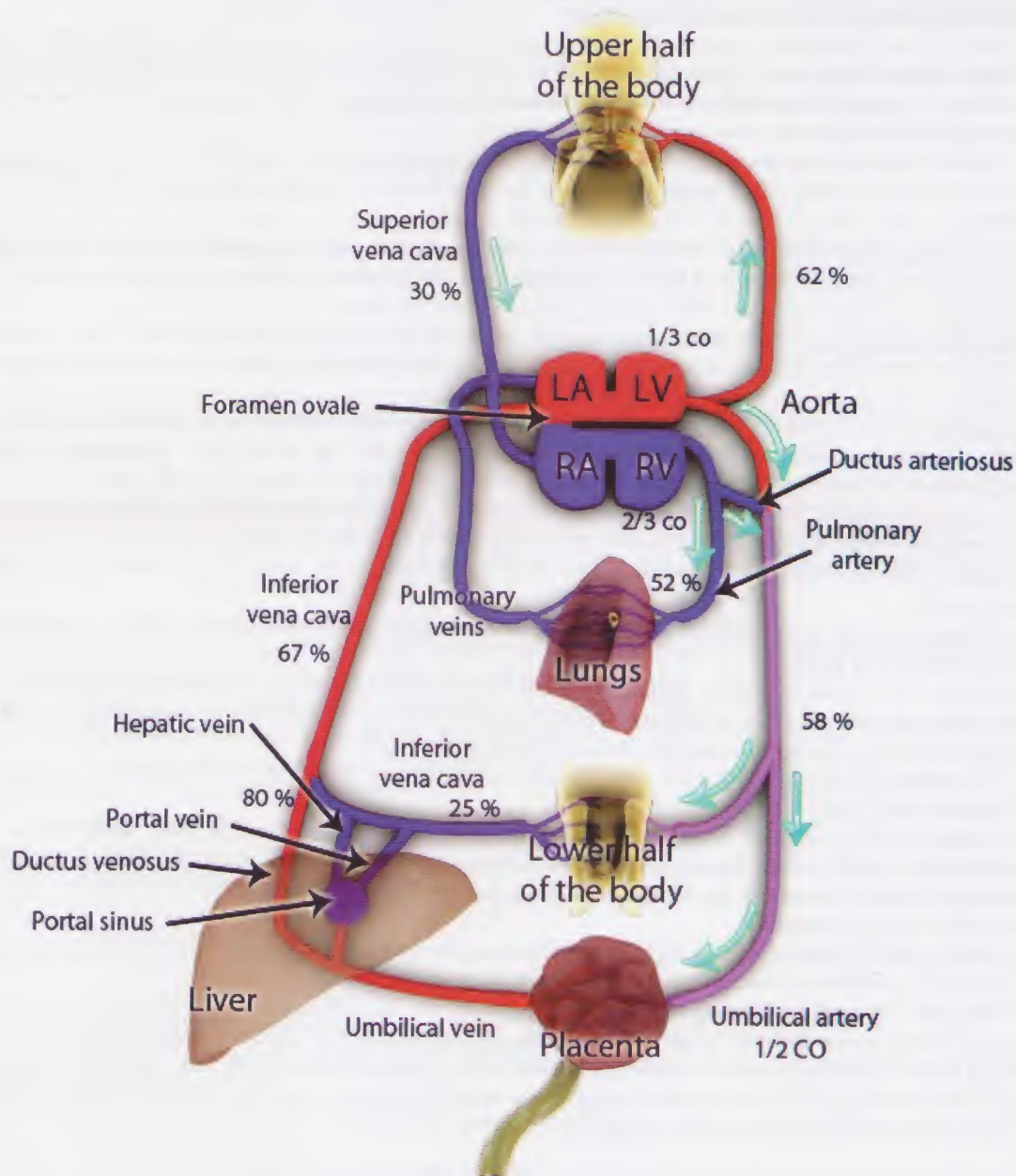
• The parallel circulation has unequal ventricular flows;

The right ventricle ejects $\frac{2}{3}$ of the combined ventricular outputs (66%).

The left ventricle ejects $\frac{1}{3}$ of the combined ventricular outputs (34%).

B) Fetal Lung

• In contrast to the fetal circulation, which is established very early during intra-uterine life, maturation of the lungs lags behind. **Extra-uterine life is not possible until after 24-26 weeks of gestation**, when **pulmonary capillaries are formed** and come to lie in close approximation to an immature alveolar epithelium.



■ Oxygenated
■ Deoxygenated
■ Mixed
 % Oxygen saturation

CO Cardiac output
 LA Left atrium
 RA Right atrium
 LV Left ventricle
 RV Right ventricle

Figure 11-1: Fetal Circulation

• At 30 weeks, the cuboidal alveolar epithelium flattens out and begins to produce **pulmonary surfactant**. This substance provides alveolar stability and is necessary to maintain normal lung expansion after birth. Sufficient pulmonary surfactant is usually present **after 34-38 weeks of gestation**. Administration of corticosteroids to the mother can **accelerate** fetal surfactant production.

Physiological Transition of the Fetus at Birth

1- During Expulsion of the Fetus at Delivery:

The chest wall and lungs are squeezed by the forces of the pelvic muscles and the vagina acting on the body (**the vaginal squeeze**); therefore, **the fluid** which is normally present **in the fetal lung** at term (about 90 mL of plasma ultra-filtrate) is **squeezed from the fetal lungs**. Any remaining fluid is reabsorbed by the pulmonary capillaries and lymphatics.

N.B.: Small (preterm) neonates and neonates delivered by cesarean section do not benefit from the vaginal squeeze and thus typically have greater difficulty in maintaining respiration (**transient tachypnea of the newborn**).

2- Recoil of the Chest Wall after compression by vaginal squeeze assists **expansion** of the lungs against forces of surface tension; therefore, functional residual capacity reaches 75% of its ultimate volume in a few minutes.

3- Hypoxia, Acidosis, and Sensory Stimulation by cord clamping, pain, noise, and touch produce **initiation of respiratory efforts**, normally within 30 seconds after birth, and become sustained within 90 seconds.

4- By the effect of 1, 2, and 3, **increased alveolar and arterial O₂ tension from fetal values (fetal PaO₂) 15-25 mm Hg to neonatal values (neonatal PaO₂) 65-97 mm Hg stimulates pulmonary arterial vasodilatation** decreasing the pulmonary vascular resistance. This increases the pulmonary blood flow and increases the blood flow to the left heart; therefore, **the left atrial pressure is increased and the right atrial pressure is decreased** causing **functional closure of the foramen ovale** by the onset of ventilation (anatomical closure occurs at 3 months to one year of age and 20% of children remain probe patent foramen ovale).

Also, **clamping of the umbilical cord** increases systemic vascular resistance which **helps to maintain the increased left atrial pressure**.

On closure of the foramen ovale, blood from the venae cavae (superior and inferior) enters the right atrium then passes to the right ventricle reaching the pulmonary circulation. The pulmonary blood flow is increased helped by the low pulmonary vascular resistance.

N.B.: The instant the umbilical cord is cut, the fetus becomes physiologically and legally an independent and separate individual.

5- Increased PaO₂ > 60 mm Hg and chemical mediators such as acetylcholine, bradykinins, and prostaglandins produce **functional closure of the ductus arteriosus**. This occurs **10-15 hours after birth** (**anatomical closure occurs at 4-6 weeks of life**). In the first hours, there may be bi-directional shunting through the ductus arteriosus.

The overall result is elimination of right to left shunting by functional closure of both the foramen ovale and the ductus arteriosus resulting in establishment of adult circulation.

N.B.: **Hypoxia or acidosis during the first few days of life** can prevent or reverse these physiological changes, leading to **persistence of (or return to) the fetal circulation**. A vicious circle is established where the right to left shunting promotes more hypoxemia and acidosis which in turn promotes more shunting. Right to left shunting may occur across the foramen ovale, the ductus arteriosus or both. Unless this circle is broken, neonatal demise can occur rapidly.

Fetal and neonatal resuscitation can be started before and even during delivery.

A) Antepartum Fetal Evaluation and Resuscitation

Aim: Antepartum detection of fetal and maternal factors that can affect the fetus. These factors are associated with the need for neonatal resuscitation.

a- Maternal Factors: such as:

Maternal diabetes, pregnancy induced hypertension, chronic hypertension, previous Rh-sensitization, previous still birth, bleeding in the 2nd or 3rd trimester, maternal infections, lack of prenatal care, maternal substance abuse and maternal drug therapy e.g., reserpine, lithium, carbonate, Mg, and adrenergic-blockers.

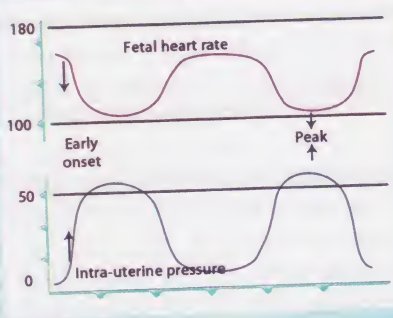
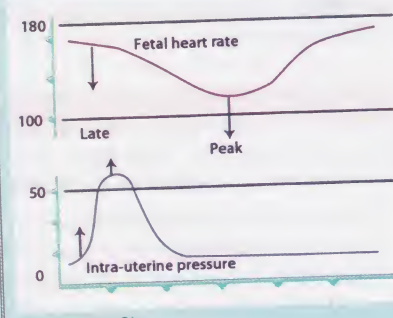
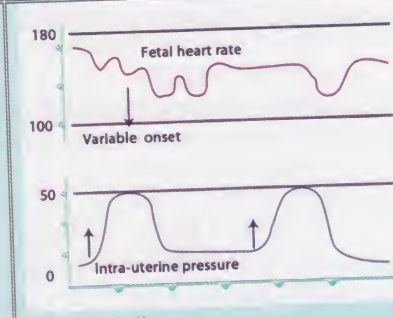
b- Fetal Factors: such as:

Known fetal anomalies, post-term or pre-term gestation (i.e., born less than 37 weeks after the last menstrual period), multiple gestation, size-date discrepancy, intrauterine growth retardation (i.e., small for gestational age), and poly- and oligo-hydramnios.

It is reduced (i.e., there is smooth line in the trace) due to the following causes: fetal distress (acidosis, hypoxia), prematurity, fetal sleep cycles, central nervous system damage as anencephaly, and maternal

drugs as anticholinergics (with increased fetal heart rate), central nervous depressant drugs such as opioids, barbiturates, benzodiazepines, Mg sulfate, and local anesthetics (as in lumbar epidural analgesia).

3. Deceleration patterns: It is a relation of fetal heart rate to uterine contractions.

Type	Definition and Value	Cause	Figures
Early (type I) decelerations (figure 11-2)	<ul style="list-style-type: none"> - The decreased fetal heart rate is of early onset occurring with the onset of uterine contractions. Their peaks coincide with the peaks of uterine contractions and they have uniform shapes (i.e., a mirror image of the uterine contractions). - Fetal heart rate is decreased by about 10-20 beat/min (fetal heart rate does not decrease below 100 beat/min). 	Vagal response to compression of the fetal head or stretching of the neck during uterine contractions (it is not due to fetal distress). N.B.: It is not abolished by increasing fetal oxygenation, but is blunted by the administration of atropine.	 <p>(figure 11-2)</p>
Late (type II) decelerations (figure 11-3)	<ul style="list-style-type: none"> - The decreased fetal heart rate is of late onset after the onset of uterine contractions by 10-30 seconds. Their peaks occur after the peaks of uterine contractions and they have a uniform shape. 	Fetal distress (fetal hypoxia) due to decreased utero-placental blood flow N.B.: It is improved (abolished) by increasing fetal oxygenation, changing the maternal position, i.v. fluids, stopping uterine contractions by stopping oxytocin infusion; otherwise, delivery is needed.	 <p>(figure 11-3)</p>
Variable (type III) deceleration The most common (figure 11-4)	<ul style="list-style-type: none"> - It is variable in onset, duration and peak in relation to uterine contractions. - Fetal heart rate changes by about > 30 beat/min and fetal heart rate is usually <100 beat/min. 	Umbilical cord compression N.B.: Increased fetal O ₂ has no effect, but atropine decreases this pattern.	 <p>(figure 11-4)</p>

b- Fetal Blood Sampling: is obtained by a small scalp puncture.

It is indicated when an abnormal fetal heart rate pattern persists.

- pH 7.25-7.35 indicates a normal vigorous neonate.
- pH 7.20- 7.25 indicates a borderline abnormality and sampling should be repeated 30 minutes later.
- pH < 7.20 indicates significant neonatal acidosis and depression requiring urgent delivery of the baby.

c- Fetal Pulse Oximetry:

It is a newer technique evaluating intrapartum fetal oxygenation as it provides continuous fetal arterial O₂ saturation readings. The probe is placed through the cervix to lie alongside the fetal cheek or temple.

Normal fetal O₂ saturation ranges between 30% and 70%.

Saturation less than 30% indicates fetal hypoxia.

d- Ultrasonography:

During labor, it is mainly used to:

- determine the fetal presenting part.
- confirm intrauterine fetal health or demise, if fetal heart rate tones are not heard.
- determine the quality of amniotic fluid present in the uterus.
- diagnose placental abruption and placenta previa.
- obtain an umbilical cord sample for arterial blood gas analysis.

Values (arterial): ▫ Normal-7.25-7.35. There is good agreement between Apgar and cord PH.

- Low normal PH should be repeated in 30 min.
- Values between 7.2 and 7.24 need further evaluation.
- Less than 7.20 indicates significant asphyxia which necessitates immediate delivery.

Intrapartum Management (or Resuscitation):

1- **Treatment of the cause**, for example:

- Correction of the factors that decrease O₂ delivery to the fetus such as maternal hypotension (by i.v. fluids and ephedrine), low cardiac output, aorto-caval compression, sympathectomy, hemorrhage, cardiac disease, and decreased O₂ in mothers as in asthma, pneumonias, or pulmonary edema.
- Correction of the factors that decrease blood flow to the fetus such as hyperstimulation, or tetany by stopping of oxytocin infusion and adding tocolytics. Placental abruption, and rupture uterus need immediate delivery.
- Saline amnio-infusion may be done by infusion of saline into the uterus via an intrauterine catheter to relieve cord compression or dilute thick meconium. This decreases meconium-aspiration syndrome.

2- **Oxygen supplementation.**

3- **Persistent** evidence of fetal distress **necessitates immediate delivery.**

Urgency of delivery is guided by the results of fetal monitoring. Urgency of cesarean section delivery is classified into the following 4 grades:

Grade 1: Emergency: immediate threat to life of woman or fetus.

Grade 2: Urgent: maternal or fetal compromise which is not immediately life-threatening.

Grade 3: Scheduled: needing early delivery, but with no maternal or fetal compromise.

Grade 4: Elective: at a time to suit the patient and the maternity team.

C) Postpartum Neonatal Evaluation and Resuscitation (at Birth)

It is usually done by obstetricians, pediatricians or nurse specialists. The anesthesiologist may be requested to provide brief assistance in resuscitation, but that must not be on expense of mother care. During care of a depressed neonate, at least 2 persons must be available for respiratory resuscitation and cardiac resuscitation with/without 3rd one for giving i.v. fluids and drugs. Neonatal resuscitation equipment and drugs should be readily available in the delivery room.

Protocol of Neonatal Resuscitation

Recommended in 2000 by the American Heart Association/American Academy of Pediatrics (figure 11-5).

Artificial Positive Pressure Ventilation of the Newly Born Neonate

Indications:

- Persistent apnea or inadequate respiration i.e., persistent cyanosis in spite of giving 100% O₂ by mask.
- Persistent bradycardia < 100/min.
- Cardiac arrest.
- Apgar score 0-2.

Technique:

Ventilation can be performed by **Jackson Rees' modifications of Ayre's T- piece** with manual compression of the bag through:

- **A face mask.**
- **A laryngeal mask size 1** which has been used recently in resuscitation for at least 2.5 kg and 35 week gestation or larger.
- An endotracheal tube (by a **Miller** straight bladed laryngoscope size 00 or 0).
- Endotracheal tube **size** 2.5 ID is suitable for neonates < 1 kg body weight.
3.0 ID is suitable for neonates 1-2 kg body weight.
3.5 ID is suitable for neonates > 2 kg body weight.

The correct size is indicated by a small leak which occurs around the tube when the airway pressure is at 20 cm H₂O.

- Endotracheal tube **length** can be estimated by the following equation:

Tip to lip = 6 cm + body weight in kg.

The correct length should be confirmed by chest auscultation.

- Indications of intubation: □ ineffective face mask.
 □ the need for prolonged mechanical ventilation.
 □ as a route for medications.

Mechanical Ventilation:

Ventilation setting is usually:

- Respiratory rate should be 40–60/min.
- Peak inspiratory pressure: should be 30–40 cm H₂O initially to allow initial lung expansion, but later breaths should be ≤ 30 cm H₂O to avoid rupture of the lung.
- Positive expiratory airway pressure (PEEP) is adjusted 1–3 cm H₂O if possible.
- FiO₂: ventilation should be started with FiO₂ 1 (i.e., 100% O₂) then adjusted according to pulse oximetry, or arterial, capillary, or umbilical artery catheter blood gases. The aim is to keep preductal PaO₂ between 60–80 mm Hg to avoid retro-lental fibroplasia.

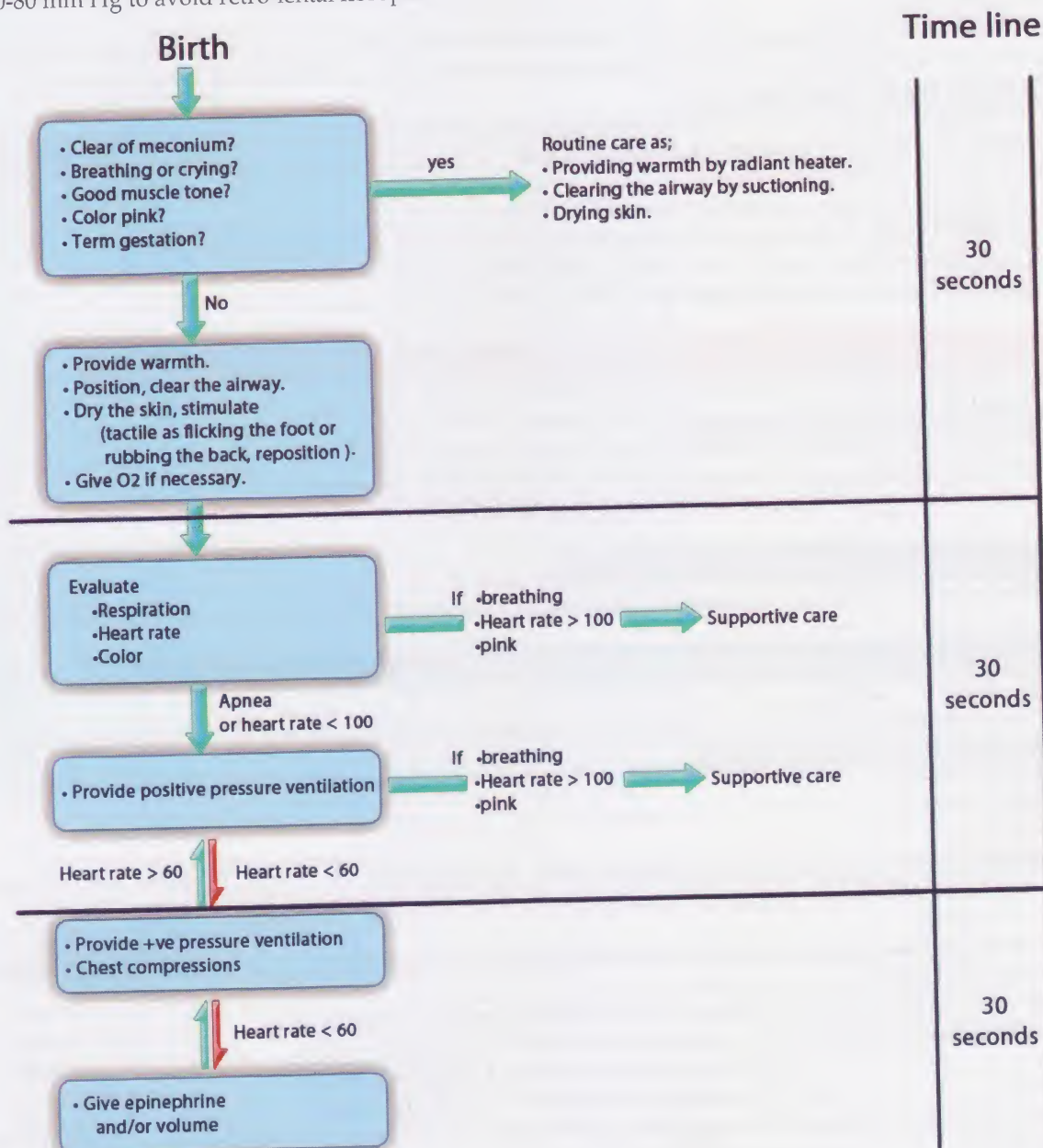


Figure 11-5: Protocol of neonatal resuscitation

Chest Compression of the Newly Born Neonate (Cardiac Resuscitation)

Indications:

- Heart rate < 60/min.
- Cardiac arrest.

Technique:

- There are two techniques:
- Both thumbs are placed at the junction of the middle and the lower 1/3 of the body of the sternum and the other fingers should encircle the body to support the back (figure 11-6)
 - or • the middle and ring finger tips are used.

The sternum should be compressed 1.5-2 cm (to a depth of about 1/3 of the antero-posterior diameter of the chest) at a rate of 90-100/min. Cardiac massage: ventilation ratio should be 3:1.



Using 2 fingers (less efficient)



Using encircling fingers

Figure 11-6: Chest compression in the newborn

Effective cardiac massage is indicated by:

- a constricted pupil
- maintained arterial blood pressure at 80 mm Hg
- or • maintained coronary perfusion detected by ECG monitoring.

Neonatal Evaluation and Assessment

1- Apgar Score:

It was described by Dr. Virginia Apgar in 1953.

Mnemonic	Signs	Score		
		0	1	2
A	Appearance (color)	Blue or cyanotic	Pink body and blue cyanotic extremities	All pink
P	Pulse (heart rate) It is normally 120-160/min by auscultating the precordium or the base of the umbilical cord.	Absent	< 100/min	> 100/min
G	Grimace (reflex irritability) It is the response to nasal catheter insertion.	Absent	Grimace	Coughing, sneezing, and crying
A	Attitude (muscle tone)	Flaccid	Some flexion of the extremities	Active motion and good flexion
R	Respiratory effort Normal respiratory rate is 30-60/min, detected by chest auscultation.	Absent	Slow and irregular	Good and strong crying

It is done at **1 minute** after birth which correlates with **survival** and **5 minutes** after birth which correlates with **neurologic outcome**.

At 1 minute assessment,

- Score 8-10 indicates vigorous normal neonates "most babies".
Nothing is needed, except **general care** as above.
- Score 5-7 indicates mildly asphyxiated neonates.
They usually respond to **vigorous stimuli and O₂** blown over their face.
If no response is detected, they should be ventilated with 80-100% O₂ by bag and mask.
- Score 3-4 indicates moderately asphyxiated neonates.
They need ventilation with **endotracheal tube** and **correction of the acidosis** by NaHCO₃.
- Score 0-2 indicates severely asphyxiated neonates.
They usually need **mechanical ventilation** and **chest compression**.

If the assessment at 5 min is < 7, do additional assessment every 5 min, until 20 min have passed or until 2 successive scores ≥ 7 .

2- Assessment of the Delayed Effect of Drugs Administered to Mothers during Labor

It is not detected by Apgar score.

a- Early Neonatal Neurobehavioral Scale:

- It evaluates the neonate's states of wakefulness, reflex responses, skeletal muscle tone, response to sound and habituation.

N.B.: Habituation is the ability of neonates to decrease their responses to stimuli. It represents the earliest example of processing information by the cerebral cortex.

- It is impaired by anesthetic drugs administered as maternal systemic medication during labor and delivery.

• General anesthesia (as compared with regional anesthesia), in elective cesarean section, causes generalized depression of neurobehavioral testing of infant despite similar Apgar scores in both groups.

b- Neurological and Adaptive Capacity Score:

- It evaluates the neonate's states of reflex responses, skeletal muscle tone, response to sound and light, and habituation.
- It provides a single numerical value to indicate a depressed or vigorous neonate.
- It is done 15 minutes after birth and repeated 2 hours later. If there are abnormalities, the score is repeated at 24 hours.

Drug Therapy in Neonatal Cardiopulmonary Resuscitation

Drugs can be administered to neonates through one of the following routes:

1. Umbilical vein (one in number).
2. Umbilical artery (two in number) (Figure 11-7).
3. Peripheral veins.
4. Endotracheal instillation: 4 drugs can be administered via the trachea "Lidocaine, Epinephrine, Atropine, and Naloxone" (LEAN) with a delayed onset and peak of action.

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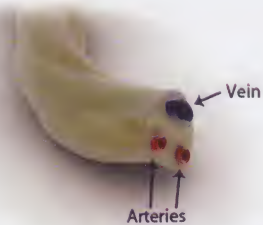


Figure 11-7: Cross-section of the umbilical cord

1- NaHCO₃:

Respiratory acidosis is corrected by continuous ventilatory support, while metabolic acidosis is corrected by **NaHCO₃ infusion**.

Dose: can be calculated according to the following equation in mEq

$$= 0.4 \times \text{Body weight in kg} \times \text{Base deficit (by arterial blood gases)}.$$

If resuscitation is prolonged > 5 min, especially if arterial blood gas analysis is not available, give 2 mEq/kg i.v. of 0.5 mEq/mL solution empirically.

Adequate ventilation should be continued before and during administration of NaHCO_3 to minimize the risk of hypertonicity and intracranial hemorrhage, which can result from rapid bicarbonate administration and accompanying increases in cerebral blood flow due to increased PaCO_2 . Therefore, NaHCO_3 should be given as 0.5 mEq/mL solution, at a slow rate < 1 mEq/kg/min.

N.B.: **Tromethamine (THAM)** is an alternative to NaHCO_3 which has the advantage of reducing PaCO_2 .

2- Epinephrine:

Indications: It is the single most useful drug even with bradycardia.

- Persistent bradycardia < 60 /min or asystole in spite of adequate ventilation and cardiac compression.
- Hypotension.

Dose: 0.01-0.03 mg/kg (0.1-0.3 mL/kg of 10 000 solution) can be repeated every 3-5 minutes, by i.v. bolus, through the umbilical artery catheter, or endotracheally in case of arrest and followed by 5 manual ventilatory cycles.

N.B.: Atropine 0.03 mg/kg can be used only for vagally mediated bradycardia. It is rarely used because bradycardia of neonates is rarely due to vagal stimulation.

Isoprenalol 0.1-1 mg/kg/min can be also used.

3- Calcium:

Indications:

- Documented hypocalcemia.
- Neonates suspected to have magnesium intoxication from mothers receiving MgSO_4 . They are hypotonic, hypotensive, and hypoventilated neonates.
- Hyperkalemia.
- Ca^{++} channel blocker excess.

Doses: Calcium chloride 30 mg/kg.

Calcium gluconate 100 mg/kg.

4- Naloxone:

Indications: It is used to reverse respiratory depression of narcotics given to the mother in the last 4 hours of labor.

In narcotic addicted mothers, it may precipitate withdrawal symptoms in neonate; so, it is not used.

Dose: 0.1 mg/kg i.v. or 0.2 mg/kg i.m., subcutaneously, or endo-tracheally in concentration of 0.4 mg/mL.

5- Glucose:

Indications: It is only used if neonatal hypoglycemia is documented because glucose increases lactic acid production which aggravates central nervous system injury.

Dose: 8 mg/kg/min or oral feeding 2-3 mL/kg $\text{D}_{10\%}$.

6- Surfactant:

Indications: It is given endotracheally to the premature neonates who have respiratory distress syndrome.

Immediate Neonatal Emergency

A) Medical Neonatal Emergency

1- Meconium Stained Neonates (and Meconium Aspiration Syndrome):

Incidence: 10% of all deliveries.

Cause: It mostly occurs after 34 weeks of gestation due to intrauterine arterial **hypoxemia** (i.e. fetal distress) which increases gut motility and **causes defecation**. This leads to presence of **meconium in the amniotic fluid** (meconium is the breakdown product of swallowed amniotic fluid, gastro-intestinal cells and secretions). Thick meconium usually occurs with severe fetal distress. With more hypoxia, **gasping** occurs, causing **inhalation of the meconium** mixed amniotic fluid which reaches the trachea and large airways i.e., **meconium aspiration**.

On initial respirations, meconium is pushed to the small airways, obstructing them and causing **ventilation/perfusion mismatching**. This leads to severe respiratory distress which occurs in 10% of meconium-stained neonates. Death usually occurs in 10% of these patients.

Clinical Picture:

- Respiratory rate is ≥ 100 /min, with presence of cyanosis.
- Lung compliance is decreased (like infant respiratory distress syndrome).

- In severe cases, pulmonary hypertension causes right to left shunting via the patent foramen ovale and ductus arteriosus i.e., there is **persistence of fetal circulation** which results in severe arterial hypoxemia.
- Pneumothorax occurs in 10% of cases (compared with 1% for all vaginal deliveries).

Treatment:

- 1- Just after delivery of the head and before shoulder delivery, **suction of the mouth, nose, and posterior pharynx** should be performed.
- 2- After complete delivery of the baby and transference to under radiant heater, **endotracheal tube** is inserted and suction is done before the 1st breath is taken. Suction can be repeated till no meconium is obtained (usually within 3 times). Intubation is not mandatory, but should be conducted according to the condition of the neonates.
- 3- O₂ should be administered by a face mask and the neonate should be managed according to the above protocol.
- 4- **Suction of the stomach** is performed to prevent passive regurgitation of any meconium.

2- Neonatal Hypovolemia:

Causes:

- 1- Early clamping of the umbilical cord or holding the neonate above the introitus before clamping of the cord.
 - 2- Twin to twin transfusion.
 - 3- Placental transection during cesarean section.
 - 4- Prematurity.
 - 5- Sepsis.
 - 6- Maternal hemorrhage.
 - 7- Fetal distress: during which larger than normal portions of fetal blood are shunted to the placenta and remain there after delivery and clamping of the umbilical cord due to presence of fetal vasoconstriction.
- N.B.: Causes of hypotension in neonates include: hypovolemia, hypoglycemia, hypocalcemia, hypomagnesemia and hypothermia.

Clinical Picture: There are signs of shock such as:

- Skin color: **pallor** that persists after oxygenation.
 - Pulse volume: **faint rapid pulse**.
 - **Cold** extremities and poor capillary refill.
 - **Arterial blood pressure: decreases** because the arterial blood pressure generally correlates with the intravascular volume in neonates. Hypovolemia is suspected if **mean blood pressure is < 50 mm Hg**.
- N.B.: Normal arterial blood pressure depends on the birth weight and ranges from 50/25 mm Hg for 1-2 kg babies to 70/40 mm Hg for > 3 kg babies.
- **Poor response to resuscitation.**

Treatment:

Intravascular volume expanders such as whole blood, plasma, 5% albumin, normal saline or lactated ringer's solution;

- Dose: 10 mL/kg over 5-10 minutes.
- Routes: one of the following routes can be used with care to avoid introduction of any air.

a- Peripheral vein cannulation.

b- Umbilical vein cannulation:

It is performed by 3.5 F or 5 F umbilical catheters. The tip of the catheters should be just below the skin level allowing free backflow of blood because more advancing of the catheter may cause liver injury by hypertonic fluid given later.

b- Umbilical artery cannulation:

It is performed by specially designed umbilical artery catheters which allow fluid and drug infusion and blood sample collection for arterial blood gas analysis.

3- Neonatal Hypoglycemia:

Causes: - Babies of diabetic mothers.

- Intrauterine growth retardation.
- After severe intrauterine fetal distress.

Clinical Picture: Hypotension, tremors and seizures.

4- Pierre Robin Syndrome:

Clinical Picture: There are glossoptosis, micrognathia, and cleft palate. Respiratory obstruction occurs when the tongue is sucked against the posterior pharyngeal wall by negative intra-pharyngeal pressure.

Treatment:

1. **Airway** should be established by oral airway or pulling the tongue forward with a clamp. The patients usually have difficult intubation.
2. **Prone position** displaces the tongue away from the posterior pharyngeal wall.
3. A small **nasopharyngeal airway** can be used to prevent negative pressure.
4. No muscle relaxant is allowed, as paralysis causes obstruction of ventilation.

5- Prematurity:

There is increased risk of:

- Respiratory distress syndrome.
- Apnea spells.
- Hypocalcemia.
- Intracranial hemorrhage.
- Kernicterus.
- Broncho-pulmonary dysplasia.
- Hypoglycemia.
- Sepsis.
- Retinopathy of Prematurity.

More details are discussed in "Pediatric anesthesia".

B) Surgical Neonatal Emergency

a- Airway Surgical Procedures:

- 1- Choanal Stenosis and Atresia.
- 2- Laryngeal Anomalies and Subglottic Stenosis.

b- Thoracic and Cardiac Surgical Procedures:

- 3- Tracheo-esophageal fistula (esophageal atresia).
- 4- Lobar emphysema.
- 5- Congenital heart diseases such as transposition of great vessels.

c- Abdominal or Gastrointestinal Surgical Procedures:

- 6- Congenital diaphragmatic hernia.
- 7- Abdominal wall defects (gastroschisis or omphalocele).
- 8- Pyloric stenosis or intestinal atresia.
- 9- Necrotizing entero-colitis.
- 10- Malrotation or midgut volvulus.
- 11- Repair of inguinal hernia.
- 12- Imperforate anus.
- 13- Hirschsprung's disease.
- 14- Congenital hyperinsulinism.

These diseases are discussed in the chapter of "Pediatric Diseases".

Q: What are the anesthetic managements of neonatal emergencies?

A: Discuss medical and surgical neonatal emergencies.

Q: What are the anesthetic managements of surgical neonatal emergencies?

A: Discuss surgical neonatal emergencies.

Further Readings

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